# Statistical Analysis Plan Amendment 3

**Study ID:** 219516

**Official Title of Study:** A Phase 3b, multicenter, single-arm, open-label study evaluating the efficacy, safety, and tolerability of switching to DTG/3TC single tablet regimen administered once daily from a bictegravir/emtricitabine/tenofovir alafenamide single tablet regimen in people living with HIV of at least 50 years of age who are virologically suppressed

**NCT number:** NCT05911360

**Date of Document:** 12-Sep-2025

| **Information Type:** | Statistical Analysis Plan (SAP) |
|---|---|

# TITLE PAGE

| | |
|---|---|
| **Protocol Title:** | A Phase 3b, multicenter, single-arm, open-label study evaluating the efficacy, safety, and tolerability of switching to DTG/3TC single tablet regimen administered once daily from a bictegravir/emtricitabine/tenofovir alafenamide single tablet regimen in people living with HIV of at least 50 years of age who are virologically suppressed |
| **Study Number:** | 219516 |
| **Compound Number:** | GSK3515864 |
| **Abbreviated Title:** | Ph 3b, BIC/FTC/TAF to DTG/3TC FDC, 96 Week switch, efficacy, safety, and tolerability study in ART-experienced older adults living with HIV with virologic suppression |
| **Acronym:** | **EYEWITNESS**: h**E**alth**Y** ag**E**ing **WIT**h dovato amo**N**g div**E**r**S**e population**S** |

**Sponsor Name:** ViiV Healthcare

**EU CT Number:** 2022-503137-66-00

**Statistical Analysis Plan (SAP) for study 219516 v3.0**

©2025 ViiV Healthcare group of companies or its licensor.

# TABLE OF CONTENTS

# LIST OF TABLES

**PAGE**

## LIST OF FIGURES

**PAGE**

# VERSION HISTORY

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP | 07 Nov 2023 | Amendment 02, dated 12 OCT 2023 | Not Applicable | Not Applicable |
| SAP Amendment 01 | 09 Sept 2024 | Amendment 02, dated 12 OCT 2023 | Added eCOA compliance section | |
| SAP Amendment 02 | 18 Mar 2025 | Amendment 03, dated 30 SEP 2024 | Removal of week 24 interim analysis, reference to supplementary analysis SAP, update of analysis sets, addition of sub-study, additional minor updates | To be consistent with protocol amendment 3 |
| SAP Amendment 03 | 12 Sep 2025 | Amendment 03, dated 30 SEP 2024 | Updated to include ad hoc requests, additional updates | |

# 1. INTRODUCTION

Contemporary potent 3-drug antiretroviral (ARV) treatment has led to remarkable declines in morbidity and mortality in treated people living with human immunodeficiency virus (HIV) leading to longer life expectancy. This longer life expectancy has been accompanied by higher rates of non-acquired immune deficiency syndrome (non-AIDS)-defining events (NADEs) such as cardiovascular disease, liver disease, and cancer. These NADEs are now the leading cause of morbidity and mortality among treated people living with HIV. The etiologies of these NADEs are multi-factorial and may include chronic inflammation and immune activation, behavioral, and lifestyle-related factors, co-morbidities and the adverse effects of antiretroviral therapy (ART). In addition, as people living with HIV live longer, aging-associated co-morbidities are being seen with greater frequency, and this multi-morbidity often requires concomitant use of other medications.

As ART needs to be taken lifelong, there is an unmet need for streamlined regimens that can minimize ART-related long-term toxicities and drug-drug interaction (DDI) while maintaining viral suppression. Even modest improvements in side effects have the potential to improve tolerability and increase adherence to lifelong treatment regimens. Living long-term with HIV and ART, even when clinically well-controlled, is associated with premature onset of chronic conditions such as heart and kidney disease, frailty, and neurocognitive impairments. This may represent premature or accelerated aging linked to HIV infection itself and pre-ART disease acute infection and set-points characteristics, but may also potentially be linked to some long-term ART toxicity. Second generation integrase strand transfer inhibitors (INSTI)s (dolutegravir (DTG) and bictegravir (BIC)) as well as the nucleoside reverse transcriptase inhibitor (NRTI) (tenofovir alafenamide (TAF)) have been shown to be independently associated with weight gain with a potential additive effect of the association of a second generation INSTI and TAF [Kanters, 2022]. TAF has also been associated with an unfavorable lipid profile compared to tenofovir disoproxil fumarate (TDF) [Mallon, 2021] or DTG [Osiyemi, 2022].

Switching from the 3-drug regimen Biktarvy (BIC/Emtricitabine (FTC)/TAF) to the 2-drug regimen (2DR) Dovato (DTG/Lamivudine (3TC) fixed-dose combination (FDC)) may therefore limit the worsening of the above metabolic parameters and improve overall health, especially in older adults living with HIV. Further, it will reduce the number of antiretroviral agents to which a participant is chronically exposed and has the potential benefit of reducing potential long-term treatment-associated toxicity and decreasing the likelihood of DDIs and costs.

Current HIV treatment guidelines recommend the 2DR DTG/3TC as an initial treatment regimen based on results from the phase 3 GEMINI-1/GEMINI-2 studies [Cahn, 2022] in switch settings in ART-experienced virologically suppressed people living with HIV based on the phase 3 SALSA and TANGO studies [Llibre, 2022; van, 2020; Osiyemi, 2022].

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Protocol 219516. Following protocol amendment 3, a sub-study was added, the virologic management/withdrawal criteria was

updated, the interim analysis at week 24 was removed and an iSRC was added to the study. Further information on the iSRC can be found protocol Section 8.3.9. Details of the sub-study and corresponding analyses can be found in Section 6.7.

Additional analyses to evaluate the results of HIV-RNA retests will be detailed in a supplementary analysis plan. These analyses will be conducted by GSK.

**Table 1 Protocol Revisions**

| **Revision Chronology:** | | |
|---|---|---|
| 219516 | 22-FEB-2023 | Original Protocol |
| | 10-MAY-2023 | Protocol Amendment 01 |
| | 12-OCT-2023 | Protocol Amendment 02 |
| | 30-SEP-2024 | Protocol Amendment 03 |

## 1.1. Objectives, Estimands and Endpoints

**Table 2 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the maintenance of virologic suppression of DTG/3TC at Week 48 post-switch from BIC/FTC/TAF | • Participants with plasma HIV-1 ribonucleic acid (RNA) ≥50 copies/mL (Snapshot algorithm) at Week 48 |
| Secondary | |
| • To evaluate the antiviral activity, immunologic effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG/3TC over time | • Participants with plasma HIV-1 RNA ≥ 50 copies/mL (Snapshot algorithm) at 24 and 96 weeks<br>• Participants with plasma HIV-1 RNA < 50 copies/mL (Snapshot algorithm) at 24, 48 and 96 weeks<br>• Absolute values and changes from baseline in CD4+ cells count and CD4:CD8 ratio at 24, 48 and 96 weeks<br>• Occurrence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48 and 96 |
| • To assess viral resistance in participants experiencing protocol-defined virologic failure over time | • Occurrence of viral resistance in participants meeting confirmed virologic withdrawal over time |
| • To evaluate the safety and tolerability of DTG/3TC over time | • Occurrence of DTG/3TC-non-Serious Adverse drug-related reactions, all serious adverse events (SAEs) and proportion of participants who discontinue treatment due to adverse events (AEs) |
| Exploratory | |
| • To evaluate the efficacy and immunologic response of DTG/3TC by participant characteristics subgroups (e.g., demographic factors, Baseline CD4, CD4 nadir) and | • Participants with plasma HIV-1 RNA < 50 copies/mL (Snapshot algorithm) at 24, 48 and 96 weeks by subgroups and pre-defined target population |

| Objectives | Endpoints |
|---|---|
| pre-specified target population (≥ 65 years old, women, non-white race, cardiovascular (CV) risk, comedication) over time | • Absolute values and changes from baseline in CD4+ cells count and CD4:CD8 ratio at 24, 48 and 96 weeks by subgroups and pre-defined target population<br>• Occurrence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48 and 96 by subgroups and pre-defined target population |
| • To evaluate further safety and tolerability parameters of DTG/3TC over time | • Incidence and severity of AEs and laboratory abnormalities over time through Week 96 |
| • To evaluate renal (in urine and blood) and bone (in blood) biomarkers over time | • Change from Baseline (Day 1) in renal and bone biomarkers at Weeks 48 and 96<br>• Changes from baseline in estimated glomerular filtration rate (Creatinine and Cystatin C Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) uncorrected for Race) and urinary protein/creatinine at 48 and 96 weeks |
| • To evaluate insulin resistance over time | • Change from Baseline (Day 1) in fasting insulin, fasting glucose, glycated hemoglobin (HbA1c) and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 48 and 96 |
| • To evaluate liver health (including fibrosis and steatosis) over time | • Change from baseline in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) levels and liver fibroscan scores (controlled attenuation parameter (CAP) score and fibrosis score) at Weeks 48 and 96 |
| • To evaluate cardiovascular risk over time | • Change from Baseline in Framingham and the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cardiovascular risk scores at Weeks 48 and 96<br>• Change from Baseline in systolic and diastolic blood pressure at Week 24, 48 and 96 |
| • To evaluate fasting lipids over time | • Change from baseline in total, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, triglycerides and total cholesterol (TC)/HDL ratio at 24, 48 and 96 weeks |
| • To evaluate weight and body morphology evolution over time | • Absolute weight and body mass index (BMI) change and proportion of participants with weight change > 5% and > 10% from baseline at 24, 48 and 96 weeks<br>• Change from baseline in total and regional (trunk and limbs) fat and lean (fat-free) mass by dual-X-absorptiometry (DXA) at 48 and 96 weeks in a subset of participant performing DXA scans<br>• Change from Baseline in Waist to Height and Waist to Hip ratio at Weeks 24, 48 and 96 |

| Objectives | Endpoints |
|---|---|
| • To evaluate control of appetite over time using the Control of Eating Questionnaire (CoEQ) respectively | • Change from baseline in CoEQ score at Weeks 24, 48, and 96 |
| • To evaluate baseline menopausal symptoms among women participants | • Baseline score using the Menopause Rating Scale (MRS) health-related quality of life (QoL) questionnaire |
| • To assess participant reported treatment satisfaction | • Change from baseline in HIV Treatment Satisfaction Questionnaire status version (HIVTSQs) and HIV Treatment Satisfaction Questionnaire change version (HIVTSQc) total treatment satisfaction score and individual responses at 24, 48 and 96 weeks |
| • To assess bother from HIV-related symptoms | • Change from baseline in bothersome symptoms using the Symptom Distress Module at 24, 48 and 96 weeks |
| • To assess health-related quality of life | • Change from baseline in health-related quality of life using the World Health Organization Quality of Life (WHOQOL)-HIV BREF at 24, 48 and 96 weeks |
| • To evaluate participants' motivations for switching to DTG/3TC within a clinical trial and their treatment aspirations of less medicine*<br><br>• To evaluate investigators' motivations for switching participants to DTG/3TC within a clinical trial and assess the ease of switch* | • At baseline, ask participants the reasons for switching to DTG/3TC using a ViiV developed questionnaire. At weeks 24, 48 and 96, repeat select questions to assess if baseline aspirations are being met. Qualitative interviews** will also be conducted to further understand participants motivations at baseline and weeks 24, 48 and 96<br>• At baseline, ask investigators the reasons for switching participants to DTG/3TC using a ViiV developed questionnaire. At weeks 24, 48 and 96, assess the ease of switch and experience of the use of DTG/3TC. Qualitative interviews will also be conducted to further understand investigator motivations and experience at baseline and weeks 24, 48 and 96 |
| • To explore Pre-switch (≥ 24 weeks post-BIC/FTC/TAF initiation and up to -48 weeks to Day 1) and Week 24, 48 and Week 96 post-Switch slopes of the following endpoints where sufficient data available† | • Weight and BMI based on available data collected retrospectively in the pre-switch period<br>• Lipids (total, HDL and LDL cholesterol, triglycerides) based on available data collected retrospectively in the pre-switch period<br>• Liver Chemistry (ALT, AST) based on available data collected retrospectively in the pre-switch period<br>• Blood Hematology (CD4, CD8 and Platelet counts) and Clinical Chemistry (Fasting glucose, HbA1c, insulin and Creatinine) based on available data collected retrospectively in the pre-switch period |
| • To evaluate the acceptability, uptake and utility of the Liverpool Combined Co-Morbidity | • Summary data of provider questionnaires at Week 24, Week 48 and Week 96 |

| Objectives | Endpoints |
|---|---|
| Risk Calculator in clinical practice in countries where the tool is implemented* | • Thematic output of provider (support staff, nurses, and physicians) qualitative interviews at Week 24, Week 48 and Week 96 |
| • To evaluate the acceptability, uptake and utility of participant leaflet among participants and providers* | • Summary data of participant and provider questionnaires<br>• Participant questionnaire - Day 1, Week 24, 48<br>• Provider questionnaire - Day 1, Week 24, 48<br>• Thematic output of patient and provider qualitative interviews**<br>• Participant qualitative interviews - Day 1, Week 24, 48**<br>• Provider qualitative interviews - Day 1, Week 24, 48** |
| • To evaluate the uptake, acceptability, utility, persistence and adherence of Actigraphy and self-reporting of behaviors (participant watch and App)*<br>• To explore sleep quality, physical activity and health behaviors (alcohol intake, mood, water intake, stress level) as collected via Actigraphy and the study App* | • Summary data of Participant Survey: Day 1, Week 24, 48 and 96<br>• Thematic output of Participant qualitative interviews**: Day 1, Week 24, 48, 96<br>• Descriptive statistics of endpoints related to sleep quality, physical activity and health behaviors (alcohol intake, mood, water intake, stress levels) |

*These objectives will be discussed in a separate analysis plan for implementation science.
**Participant and Provider qualitative interviews will only be conducted in the US, UK and Canada.
†This objective is not in scope for this analysis plan.

### 1.1.1. Primary Estimands

The primary efficacy estimand aims to evaluate virological failure with DTG/3TC at Week 48 post-switch from BIC/FTC/TAF in virologically suppressed people living with HIV of at least 50 years of age.

**Table 3 Virological Failure Estimand**

| | |
|---|---|
| Population | People living with HIV of at least 50 years of age who are virologically suppressed on Biktarvy (BIC/FTC/TAF) |
| Treatment | DTG/3TC FDC (Dovato) administered once daily over 48 weeks post-switch from Biktarvy (BIC/FTC/TAF) administered orally once daily |
| Intercurrent Events | Study treatment discontinuation due to lack of efficacy or other reasons that impact the viral load outcome: Composite strategy.<br>*Rationale*: The presence of missing data due to lack of efficacy or discontinuation for other reasons on the primary endpoint is adequately accounted for in the Snapshot Algorithm which frames the outcome around these events.<br>See Section 6.5 for full details on Snapshot Algorithm. |
| Endpoint | Participant with virologic failure (plasma HIV-1 RNA ≥ 50 c/mL as per Snapshot algorithm at 48 weeks) |

| | |
|---|---|
| Summary measures | Number and percentage of participants with virologic failure (plasma HIV-1 RNA ≥ 50 c/mL as per Snapshot algorithm at 48 weeks), within group 95% confidence interval using Exact (e.g., Clopper-Pearson) methodology |

### 1.1.2. Key Secondary Estimands

The key secondary efficacy estimand is to evaluate virological suppression with DTG/3TC at Week 48 post-switch from BIC/FTC/TAF in virologically suppressed people living with HIV of at least 50 years of age.

**Table 4 Virological Suppression Estimand**

| | |
|---|---|
| Population | People living with HIV of at least 50 years of age whose virus is virologically suppressed on Biktarvy (BIC/FTC/TAF) |
| Treatment | DTG/3TC FDC (Dovato) administered once daily over 48 weeks post-switch from Biktarvy (BIC/FTC/TAF) administered orally once daily |
| Intercurrent Events | Study treatment discontinuation due to lack of efficacy or other reasons that impact the viral load outcome: Composite strategy.<br>*Rationale*: The presence of missing data due to lack of efficacy or discontinuation for other reasons on the primary endpoint is adequately accounted for in the Snapshot Algorithm which frames the outcome around these events.<br>See Section 6.5 for full details on Snapshot Algorithm. |
| Endpoint | Participants with virologic suppression (plasma HIV-1 RNA < 50 c/mL as per Snapshot algorithm at 48 weeks) |
| Summary measures | Number and percentage of participants with virologic suppression (plasma HIV-1 RNA < 50 copies/mL as per Snapshot algorithm at 48 weeks), within group 95% confidence interval using Wilson-Score methodology |

#### 1.1.2.1. Safety Estimands

Key safety estimands include drug-related adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation over time through Week 96.

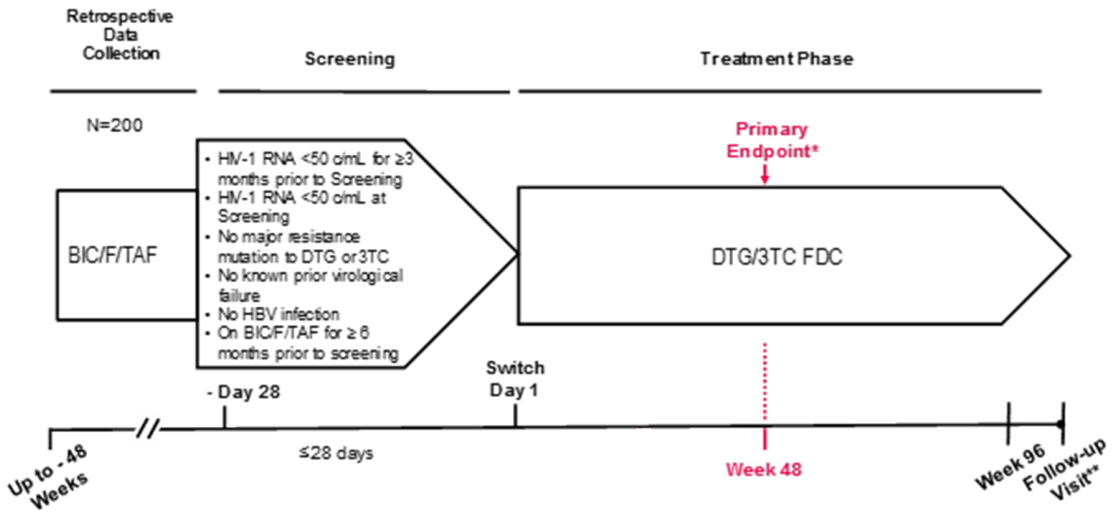
**Table 5 Safety Estimands**

| | |
|---|---|
| Population | People living with HIV of at least 50 years of age whose virus is virologically suppressed on Biktarvy (BIC/FTC/TAF) |
| Treatment | DTG/3TC FDC (Dovato) administered once daily over 48 weeks post-switch from Biktarvy (BIC/FTC/TAF) administered orally once daily |
| Intercurrent Events | • Treatment discontinuation due to any reason: treatment policy strategy<br>• Prohibited medication use: treatment policy strategy<br>Rationale: Safety data will be monitored throughout the study after the start of treatment. There is interest in evaluating and reporting safety events regardless of whether participants have completed treatment course or not and regardless of the use of prohibited medication. All safety data will be included |

| | |
|---|---|
| | up to the end of follow-up regardless of the occurrence of these intercurrent events. |
| Endpoints | • Occurrence and severity of drug-related AEs over time through Week 96<br>• Occurrence of SAEs over time through Week 96<br>• Participants who discontinue treatment due to AEs over time through Week 96 |
| Summary measures | Frequency and percentage of participants |

## 1.2. Study Design

### Table 6 Overview of Study Design and Key Features




* Primary Endpoint: participants with plasma HIV-1 RNA ≥50 copies/mL at week 48 (Snapshot algorithm)

** Follow-up Visit: to be conducted approximately 2-4 weeks after the last dose of study medication for participants who meet specific criteria. Refer to Section 4.4.1.

| | |
|---|---|
| **Design Features** | This is a Phase 3b, multicenter, single-arm, open-label study evaluating the efficacy, safety, and tolerability of switching to DTG/3TC FDC administered once daily from a BIC/FTC/TAF FDC in people living with HIV of at least 50 years of age who are virologically suppressed (VS). The study will include:<br>• A Retrospective Data Collection Phase after obtaining the participant's consent for study participation of approximately ≥24 weeks post-BIC/FTC/TAF initiation and up to 48 weeks to screening: for data such as weight, BMI, vital signs, laboratory, disease and safety parameters.<br>• A Screening Phase of approximately 28 days prior to Day 1 Visit.<br>• A Switch Treatment Phase at the enrollment visit (Day 1) up to Week 96: all eligible participants will switch from BIC/FTC/TAF to DTG/3TC FDC once daily and complete study visits at Day 1 and Weeks 4, 12, 24, 48, 72, 96.<br>• A Safety Follow-Up visit will be conducted 2-4 weeks after the last dose of study intervention for participants who meet specific criteria as described in Protocol Amendment 3 Section 4.4.1. Only the assessments necessary to evaluate the AE/SAE/laboratory abnormality should be collected. |

| | |
|---|---|
| **Study Intervention/Dosing** | Participants will receive DTG (50mg)/3TC (300mg) FDC tablet once daily to be taken orally. |
| **Time and Events** | Refer to Section 6.4: Appendix 3 Schedule of Activities. |
| **Study Intervention Assignment** | Assuming a 20% screen failure rate, approximately 250 HIV-1 infected adult participants will be screened to achieve approximately 200 enrolled participants of at least 50 years of age who are virologically suppressed on BIC/FTC/TAF FDC will switch to DTG/3TC FDC once daily for up to 96 weeks.<br>A goal of this study is to enroll populations that are traditionally underrepresented in clinical studies, including:<br>• ≥ 30% women<br>• ≥ 30% aged 65 or over<br>• ≥ 30% participants identifying as Black race<br>• ≥ 10% of Hispanic/Latinx ethnicity<br>The above diversity targets also aim at enrolling a population with a greater proportion having a ≥10% cardiovascular risk as assessed by Framingham risk score, a higher use of comedication and more comorbidities to enable subgroup analyses by these factors. |
| **Interim Analysis** | One interim analysis will be conducted after the last participant evaluable completes the Week 48 visit or prematurely discontinues from the study.<br><br>In addition, adhoc review of data by the iSRC may occur if the review threshold is met (protocol Section 8.3.9). |
| **Final Analysis** | The final analysis will be conducted after all participants complete 96 weeks (end of study [EOS]) of follow-up or prematurely discontinue the study. |

# 2. STATISTICAL HYPOTHESES

In this single arm study, no formal statistical hypothesis will be tested.

## 2.1. Multiplicity Adjustment

As there is no type 1 error, adjustment for multiplicity is not applicable. Multiple subgroups (see Section 4.6.4) will be analyzed in order to understand the treatment effect in different populations, particularly in those populations that are underrepresented. Subgroup summaries should be interpreted with caution.

# 3. ANALYSIS SETS

**Table 7 Analysis Sets**

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| Screened | • All participants who were screened for eligibility | • Study Population |
| Enrolled | • All participants who entered the study (who were enrolled or received study treatment or underwent a post screening study procedure)<br>NOTE: screening failures (who never passed screening, even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the | • Study Population |

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| | Enrolled Analysis set as they did not enter the study | |
| Assigned | • All participants who were assigned to study treatment in the study | • Study Population |
| Full Analysis Set (FAS) | • All assigned participants who received at least one dose of study treatment | • Study Population<br>• Efficacy<br>• Safety |
| Confirmed Virologic Withdrawal (CVW) | • All participants in the FAS who met Confirmed Virologic Failure Withdrawal criteria defined as: two consecutive assessments with HIV-1 RNA values ≥ 200 c/mL after Day 1. | • Efficacy<br>• Genotypic<br>• Phenotypic |
| Previous Confirmed Virologic Withdrawal (pCVW) | • All participants in the FAS who Confirmed Virologic Withdrawal (CVW) criteria defined in Protocol Amendment 2 as: one assessment with HIV-1 RNA values ≥ 200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥ 50c/mL | • Study Population<br>• Study Withdrawal<br>• Genotypic<br>• Phenotypic |
| Resistance Data (RES) | • All participants in the FAS population who have available resistance data | • Genotypic<br>• Phenotypic |
| Confirmed Virologic Withdrawal Resistance (CVWR) | • Comprised of all participants in the FAS population who met Confirmed Virologic Withdrawal (CVW) through the end of visit window and have available On-treatment resistance data at the time CVW criterion is met | • Study Population<br>• Genotypic<br>• Phenotypic |
| Non-CVW with Resistance Data (nCVW) | • All participants in the FAS population who have available resistance data but are not in the CVW or pCVW populations | • Genotypic<br>• Phenotypic |
| Potential Precautionary Virologic Withdrawal (pPVW) | • All participants in the FAS with two consecutive assessments with HIV-1 RNA ≥ 50 and < 200 copies/mL (instances where a first elevation of HIV-1 RNA ≥ 200 copies/mL followed by HIV-1 RNA ≥ 50 and < 200 copies/mL will also be considered pPVW) | • Genotypic<br>• Phenotypic |
| Precautionary Virologic Withdrawal (PVW) | • Comprised of all participants in the FAS who met pPVW and had resistance testing through the end of visit window | • Study Population<br>• Genotypic<br>• Phenotypic |
| Sub-study | • All participants who are eligible for the sub-study who provided consent to participate in sub-study | • All sub-study analyses |

# 4. STATISTICAL ANALYSES

## 4.1. General Considerations

Statistical analysis of this study as defined in this analysis plan will be the responsibility of Pharmaceutical Product Development (PPD) which is part of Thermo Fisher Scientific. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data

will be conducted as deemed appropriate. The analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDSIC) standards (Study Data Tabulation Model Implantation Guide (SDTM IG) Version 3.3 & Analysis Data Model Implementation Guide (ADaM IG) Version 1.1). For the creation of ADaM datasets (e.g., Concomitant Medication Analysis Dataset (ADCM)/Adverse Event Analysis Dataset (ADAE)), the up-to-date version of dictionary datasets will be implemented as SDTM.

All data processing, summarization, and analyses will be performed using SAS Version 9.4 or higher.

The analysis of the study will be performed as follows:

- An interim analysis (IA) after the last participant completes the Week 48 visit or prematurely discontinues from the study. This will be considered the primary analysis for the study. See Section 4.7.1 for details.
- Further additional analyses may be performed to support regulatory activities, business planning, publication, or other purposes.
- A final analysis after all participants complete Week 96 (EOS) of follow-up or prematurely discontinue from the study. See Section 4.7.2 for details.

A soft database lock refers to when the study database is considered clean, complete, and ready for a planned analysis. This will be implemented prior to the IA at Week 48 (primary analysis). Database can be further changed or amended after the planned analyses. A hard database lock follows the same procedure as a soft lock, but no further data changes or amendments are expected. This will be implemented prior to the final analysis at Week 96. Details on IAs are described in Section 4.7.

For Week 48 and 96 analyses, outputs will be presented for the Treatment Phase unless otherwise specified. Safety data presented through weeks 48 and 96, will comprise all available safety data collected at that time point. For example, if some earlier recruiting participants have reached Week 60 and have available safety data, this will be presented for the Week 48 analysis.

RTF files will be generated for all reporting efforts. All displays will use the term “participants”.

The date9. format, as commonly used in SAS, will be used for all dates. Partial dates will be presented as: MMMYYYY, YYYY, or blank for missing.

For analysis reporting:

- Actual time relative to dosing will be used in figures, summaries, and calculation of derived parameters, unless otherwise stated.
- The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- For data listings, actual time relative to study drug dosing will be shown.

- Unscheduled visits will be assigned to a study visit using the all-inclusive windows defined in Section 6.3.7. However, data summaries will only report visits that are planned assessment time points for each parameter (according to the Schedule of Activities in Section 6.4).
- Assessments at unscheduled visits will be done for "any time on-treatment" time points and in data listings, as well as any algorithm that makes use of additional data (e.g., Snapshot).
- For summaries that are proposed for Week X, X can be either 24, 48, or 96. This is to allow the same summary to be used to meet the needs of the IA at Week 48, and final analysis at Week 96.

### 4.1.1. General Methodology

This is a single-arm study. At the enrollment visit (Day 1), all eligible participants will switch from BIC/FTC/TAF to DTG/3TC FDC once daily.

A participant may withdraw consent and discontinue participation in this study at any time at his/her own request. The investigator may also, at his or her discretion, discontinue the participant from participating in this study at any time (e.g., safety, behavioral or administrative reasons). Participants who prematurely withdraw from the study will not be replaced.

Unless otherwise specified, summary statistics for continuous parameters will include n, mean, Q1, median, Q3, standard deviation, minimum, and maximum. Geometric mean and coefficient of variation (%CV) will be presented in place of arithmetic mean and standard deviation where data are log-transformed. For log-transformed data, change from baseline and percent change from baseline tables will present geometric mean ratio in place of geometric mean. All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. The minimum and maximum values will be reported to the same decimal place as the measured value. See Section 6.3: Data Derivation Rule for details on variables that requires a transformation before generating data summaries.

Categorical parameters will be summarized by frequencies and percentages of participants. Confidence intervals (CI) may be generated in addition to the summaries using Wilson-Score or Exact (e.g., Clopper-Pearson) methodology. In particular, the confidence intervals will be estimated using a 2-sided Clopper-Pearson exact test for virological failure (VF) and Wilson-Score method for virological suppression (VS).

Percentages will be rounded to one decimal place for efficacy displays and zero decimals for safety and study population displays. HIV-1 RNA results may be provided as censored values, such as <20 or >9,999,999 c/mL. For the purposes of summary statistics, such values will be replaced by the next value beyond the limit of detection, e.g., 19 or 10,000,000 c/mL, respectively, for the given examples (see Section 6.3.2 for further details). Furthermore, for laboratory data, if a laboratory value which is expected to have a numeric value has a non-detectable level reported in the database as "<x" or

">x", "≤x" or "≥x", the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. More details can be found in Section 6.3.3.

All analysis and summary tables will include the analysis population sample size (i.e., number of participants and number of participants with available data points at each visit). All listings will be sorted for presentation in order of site, participant, and date/time of procedure or event.

### 4.1.2. Baseline Definition

For all endpoint parameters (unless otherwise stated), the baseline value will be defined as the latest non-missing pre-dose assessment value (including unscheduled visits but excluding any data collected as part of the retrospective data collection). If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If baseline data are missing, no derivation will be performed, and baseline will be set to missing.
The baseline definitions specified in the table below will be used for derivations for endpoints/parameters and indicated on summaries and listings.

| Definition | Reporting Details |
|---|---|
| Change from Baseline | = Post-Dose Visit Value – Baseline |
| % Change from Baseline | = 100 x [(Post-Dose Visit Value – Baseline) / Baseline] |

### 4.1.3. Multicenter Studies

Data will be summarized for all centers combined. Country, or Country grouping (i.e., Region) may be included as an exploratory subgroup for specific endpoints, see Section 4.6.4.

## 4.2. Primary Endpoint Analysis

The primary endpoint will be analyzed based on the FAS, (i.e., all participants who received at least one dose of DTG/3TC).

### 4.2.1. Definition of endpoint

The primary endpoint is virologic failure (plasma HIV-1 RNA ≥ 50 copies/mL as per Snapshot algorithm, see Section 6.5) at 48 weeks.

Virologic outcome will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the Week 48 Window (see Section 6.3.7). The Snapshot algorithm is used to classify participants into three categories: HIV-1 RNA ≥ 50 c/mL at Week 48 Window ('Virologic failure'), HIV-1 RNA < 50 c/mL at Week 48 Window ('Virologic success') or no virologic data at Week 48 Window.

The Snapshot algorithm treats all participants without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to the visit window) as non-responders. The nature of this missing data will be further classified in Snapshot

summaries as either 'Virologic Failure' or 'No Virologic Data at Week 48'. Participants who change their ART regimen prior to the visit of interest will be considered virologic failures since changes in ART are not permitted in this protocol.

'Virologic failure' includes participants who change their ART regimen prior to Week 48 (as this is not permitted in this protocol); participants who discontinue study drug or study before Week 48 for lack or loss of efficacy, discontinue for other reasons while not < 50 copies/mL, and participants who have HIV-1 RNA ≥ 50 copies/mL at Week 48.

Virologic success includes participants who have HIV-1 RNA <50 c/mL at the visit of interest.

Virologic outcome will be summarized as a binary variable as:

- Virologic failure: Plasma HIV-1 RNA ≥ 50 copies/mL at Week 48.
- Not virologic failure: HIV-1 RNA < 50 copies/mL or no virologic data at Week 48 Window.

### 4.2.2. Main analytical approach

The frequency and percentage of participants with HIV-1 RNA ≥ 50 copies/mL per the Snapshot algorithm (see Section 6.5) will be summarized at Week 48, including within group 95% Clopper-Pearson exact confidence intervals. All virologic outcomes per the Snapshot algorithm (HIV-1 RNA ≥ 50 copies/mL, HIV-1 RNA < 50 copies/mL and No Virologic Data) will also be summarized using participant frequencies and percentages at Week X (see descriptions of X in Section 4.1).

#### 4.2.2.1. Strategy for Intercurrent Events

A composite strategy will be used for intercurrent events such as study treatment discontinuation due to lack of efficacy or other reasons that may impact the viral load outcome. They are adequately accounted for in the Snapshot algorithm, which details how to assign each participant's virologic outcome around these events.

#### 4.2.2.2. Statistical Analyses/Methods

The table below provides an overview of the planned primary efficacy analyses.

**Table 8 Overview of Planned Primary Efficacy Analyses**

| Endpoint | Summary | |
|---|---|---|
| | T | F |
| **Percent of Participants with plasma HIV-1 RNA ≥50 c/mL – Snapshot** | | |
| Study Outcome[1] based on the Snapshot at Week X | Y[2],[3] | |

**NOTES:**

- T = Table, F = Figure, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e., descriptive statistics) of the observed raw data.

[1] Study outcomes (i.e., virologic failure, virologic success (response below 50 c/mL) or no virologic data at Week X window) based on the snapshot algorithm.
[2] Generated using the 'Full Analysis Set' (primary). This table will be produced at "Week X" where X is referring to either 24, 48, or 96, to meet the needs at the Week 48 IA, and the Week 96 final analysis. It will be considered the primary analysis when X=48 whereas X=24 and 96 will be described in the secondary endpoints analyses in Section 4.3.
[3] Repeat on the following endpoint: <20 c/mL , <20 c/mL and Target Not Detected, and <20 c/mL and Target Detected.

### 4.2.3. Sensitivity analyses

DTG/3TC has been extensively studied in sponsored and non-sponsored studies in adult studies. Bayesian Dynamic Borrowing techniques or meta-analysis techniques may be explored to provide population estimates using a prior distribution of appropriate data in trials identified through a systematic literature review. The analysis will be considered exploratory, and details of the prior distribution and analysis approach will be documented in a separate technical appendix authored within GSK.

## 4.3. Secondary Endpoints Analyses

The secondary endpoints will be analyzed based on the FAS. The aim is to evaluate the antiviral activity, immunologic effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG/3TC over time.

### 4.3.1. Secondary endpoints

#### 4.3.1.1. Definition of endpoints

- Participants with plasma HIV-1 RNA ≥50 copies/mL at 24 and 96 weeks
- Participants with plasma HIV-1 RNA <50 copies/mL at 24, 48 and 96 weeks
- CD4+ cells count and CD4+:CD8+ cell counts ratio at 24, 48, and 96 weeks.
- Occurrence of disease progression (HIV-associated conditions, AIDS and death) through Weeks 24, 48 and 96

#### 4.3.1.2. Main analytical approach

- The following two summaries will be included as part of the summary described for the primary efficacy endpoint (Table 8):
  - Participants with plasma HIV-1 RNA ≥50 copies/mL using the Snapshot algorithm using frequency and percentage along with 95% CI at Week 24, 96. The 95% CI will be estimated using 2-sided Clopper-Pearson exact test.
  - Participants with plasma HIV-1 RNA <50 copies/mL using the Snapshot algorithm using frequency and percentage along with 95% CI at Week 24, 48, 96. The 95% CI will be estimated using 2-sided Wilson-Score method.

- Absolute and change from baseline in CD4+ cell count at Weeks X will be summarized using n, mean, Q1, median, Q3, standard deviation, minimum, and maximum.
- Absolute and change from baseline in CD4+/CD8+ cell count ratio at Weeks X will be summarized using n, mean, Q1, median, Q3, standard deviation, minimum, and maximum.
- Occurrence of disease progression will be evaluated through HIV-associated conditions and incidence of disease progression to stage 3 (AIDS) or death.
- HIV-associated conditions including recurrences and excluding recurrences at Weeks X will be separately summarized using frequencies and percentages. Only stage 3 events will be presented in the summaries. For the analysis purposes, the CDC HIV-1 Classification data will be derived from the eCRF page and no derivation will be performed programmatically. Please refer to Section 6.3.11 for detail descriptions of CDC HIV-1 Classifications.
- Incidence of participants who experienced disease progression to CDC Stage 3 or Death at Week X will be summarized using frequencies and percentages. In the same summary, the incidence of following progressions at Week X will also be summarized using frequencies and percentages:
  - CDC Category Stage 1 at enrollment to Stage 3 event
  - CDC Category Stage 2 at enrollment to Stage 3 event
  - CDC Category Stage 3 at enrollment to New Stage 3 event
  - CDC Category Stage 1, 2 or 3 at enrollment to Death

#### *4.3.1.2.1.* Strategy for Intercurrent Events

For the virologic suppression key secondary endpoint (plasma HIV-1 RNA <50 copies/mL), a composite strategy will be used for intercurrent events such as discontinuation due to lack of efficacy or other reasons that may impact the viral load outcome. They are adequately accounted for in the Snapshot algorithm (see Section 6.5), which details how to assign each participant's virologic outcome around these events.

Intercurrent events will not be controlled for in CD4+ cell count, CD4+/CD8+ cell count ratio, and disease progression analyses.

#### *4.3.1.2.2. Statistical Analyses/Methods*

The table below provides an overview of the planned secondary efficacy analyses.

## Table 9 Overview of Planned Secondary Efficacy Analyses

| Endpoints | Absolute Values/ Frequency and Percentages | | Change from Baseline/ Shift in Category | |
|---|---|---|---|---|
| | Summary | | Summary | |
| | T | F | T | F |
| **Percent of Participants with Plasma HIV-1 RNA ≥/ <50 c/mL– Snapshot** | | | | |
| Study Outcomes (Plasma HIV-1 RNA <50 c/mL and Plasma HIV-1 RNA <20 c/mL) at Week X by Subgroup | Y | | | |
| Proportion of Participants with Plasma HIV-1 RNA ≥/ <50 c/mL by Visit | Y[1] | | | |
| **CD4+ Cell Counts[2]** | | | | |
| CD4+ Cell Counts by Visit | Y | | Y | |
| CD4+ Cell Counts at Week X by Subgroup | Y | | Y | |
| **CD4+/CD8+ Cell Count Ratio[2]** | | | | |
| CD4+/CD8+ Cell Count Ratio by Visit | Y | | Y | |
| CD4+/CD8+ Cell Count Ratio at Week X Subgroup | Y | | Y | |
| **Post-baseline HIV-1 Disease Progression** | | | | |
| HIV Conditions including Recurrences at Week X[3] | Y | | | |
| HIV Conditions excluding Recurrences at Week X[3] | Y | | | |
| HIV Disease Progressions at Week X[4], [5] | Y | | | |
| **Confirmed Virologic Withdrawal (CVW)** | | | | |
| Cumulative Proportion of Participants Meeting Confirmed Virologic Withdrawal Criteria by Visit | Y[6] | | | |
| HIV-1 RNA Distribution at Time of Suspected and Confirmed Virologic Withdrawal | Y | | | |

**NOTES :**

- T = Table, F = Figure, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.

1. Repeated on the following endpoint: <20 c/mL and Target Not Detected, and <20 c/mL and Target Detected.
2. Using observed case (OC) data which contains the data that is available at a particular time point, with no imputation for missing values.
3. Stage 3 only.

4. HIV disease progressions categories: CDC Category Stage 1 at enrolment to Stage 3 event; CDC Category Stage 2 at enrolment to Stage 3 event; CDC Category Stage 3 at enrolment to New Stage 3 Event; CDC Category Stage 1, 2 or 3 at enrolment to Death.
5. Progression to Stage 3 or death.
6. Repeated on the following population: Previous Confirmed Virologic Withdrawal (pCVW)

**Table 10 Subgroup and Supportive Analyses**

| **Subgroup Analyses** |
|---|
| Subgroup analyses will be performed on the following:<br>• Study Outcomes (Plasma HIV-1 RNA <50 c/mL and Plasma HIV-1 RNA <20 c/mL) at Week X<br>• CD4+ Cell Counts at Week X<br>• CD4+/CD8+ Cell Count Ratio at Week X<br>The list of subgroups is provided in Table 17. |
| **Supportive Analyses** |
| • Supportive analysis based on the <50 HIV-1 RNA endpoint will be performed based on the same analysis for the following endpoints:<br>  • Percent of Participants with Plasma HIV-1 RNA <20 c/mL at Week X<br>  • Percent of Participants with Plasma HIV-1 RNA <20 c/mL and Target Not Detected Status at Week X<br>  • Percent of Participants with Plasma HIV-1 RNA <20 c/mL and Target Detected Status at Week X<br>• Proportion of participants without virologic (ERDF) or virologic/tolerability (TRDF) failure with lack of efficacy based on HIV-1 RNA ≥ 50 c/mL:<br>  • Estimated using the Kaplan-Meier nonparametric method based on the time to Confirmed Virologic Withdrawal (CVW) criteria met or treatment-related (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy)/efficacy related discontinuation (i.e., lack of efficacy).<br>  • The detailed algorithm for TRDF (and ERDF) is listed in Section 6.6.<br>  • Additional sensitivity analyses will be performed by reclassifying participants withdrawn for meeting virologic withdrawal criteria under PA02 who are not considered CVWs under PA03 as not meeting event criteria. Additional details can be found in Section 6.6.<br>  • The estimated proportion of participants without Confirmed Virologic Withdrawal and not discontinued due to treatment-related/efficacy-related reasons at Week X will be presented. |

#### 4.3.1.3. Sensitivity analyses

Sensitivity analysis is not applicable.

### 4.3.2. Additional secondary endpoint

#### 4.3.2.1. Definition of endpoint

Occurrence of viral resistance to DTG or 3TC in participants meeting confirmed virologic withdrawal criterion over time (Week 24, Week 48 and Week 96).

#### 4.3.2.2. Main analytical approach

- Virologic criteria for viral resistance testing is based on suspected virologic withdrawal (SVW) and confirmed virologic withdrawal (CVW) criteria.
  - SVW is defined as having one assessment with HIV-1 RNA ≥ 200 c/mL after Day 1. When a participant meets the criteria of SVW, their plasma samples will be collected for potential viral resistance testing for HIV-1 protease (PR),

reverse transcriptase (RT) and integrase (IN) genotype and phenotype if the participant later meets the criteria for CVW.

- CVW is defined as having two consecutive assessments of HIV-1 RNA ≥ 200 c/mL after Day 1. Prior to protocol amendment 3, CVW was defined as one assessment of HIV RNA > 200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥ 200 c/mL after Day 1.

- Previous virologic criteria for participant management regarding viral resistance testing include a previous definition of CVW (see pCVW analysis set), precautionary virologic withdrawal (PVW) and potential precautionary virologic withdrawal (pPVW). These were removed from the protocol as per Protocol Amendment 3.
  - PVW may be met after two consecutive assessments with HIV-1 RNA ≥ 50 and < 200 c/mL without an identifiable, non-virologic cause (immunization, illness, non-adherence) and after discussions with a Medical Monitor, or will be met with three consecutive assessments with HIV-1 RNA ≥ 50 and < 200 c/mL.
  - pPVW will be met after two consecutive assessments with HIV-1 RNA ≥ 50 and < 200 c/mL (instances where the first elevation of HIV-1 RNA ≥ 200 c/mL followed by HIV-1 RNA ≥ 50 and < 200 c/mL will also be considered for pPVW). Viral genotyping and phenotyping are further described in Section 6.3.12.

- The virology analyses of genotypic and phenotypic data will be based on the CVW resistance analysis set, and repeated for the pCVW resistance analysis set as well as for non-CVW participants with resistance data available. Data may also be available for participants in the pPVW analysis set meeting PVW criteria, and for participants whose last on-treatment HIV-1 RNA >= 400c/ml, regardless of confirmatory retesting. The frequencies and percentage of participants with resistance associated mutations observed while on DTG or 3TC will be summarized for the INSTI class and separately for NNRTI, NRTI and PI classes. Table 11 provides an overview of the planned virology analyses.

**Table 11 Overview of Planned Virology Analyses**

| Endpoint [1] | Summary | | Individual |
|---|---|---|---|
| | T | F | L |
| **Summary of Participant Accountability** | | | |
| Summary of Participant Accountability: Genotypes Available at or Prior to Week X | Y | | |
| Summary of Participant Accountability: Phenotypes Available at or Prior to Week X | Y | | |
| **Genotypic and Phenotypic Resistance** | | | |
| Summary of Known INSTI Resistance Associated Mutations and NRTI, NNRTI and PI Classes at Time of CVW at or Prior to Week X [2],[3],[4] | Y | | |
| Summary of Genotypic Susceptibility at Time of CVW at or Prior to Week X | Y | | |
| Summary of Phenotypic Susceptibility at Time of CVW at or Prior to Week X | Y | | |

| | | | |
|---|---|---|---|
| **Other** | | | |
| Summary of IC50 Fold Change to DTG and 3TC at Time of CVW at or Prior to Week X | Y | | |
| Virology Resistance Data [2] | | | Y |

**NOTES:**

- T = Table, F = Figure, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.

1. Presented on the following populations: Confirmed Virologic Withdrawal (CVW), Previous Confirmed Virologic Withdrawal (pCVW), and non-CVW with resistance data available.
2. Presented on the following populations: Full Analysis Set (FAS).
3. Sample used for resistance testing is performed with a 'plasma for storage' sample from the earliest viral load ≥200 c/mL (if such is available for a PVW case), or from the SVW visit (if ≥200 c/mL) for a CVW case, or from the CVW visit which would be >= 200 c/mL, and only tested once virologic failure for one of the above reasons is confirmed.
4. Separate outputs for INSTI and NRTI/NNRTI/PI mutations.

## 4.4. Exploratory Endpoint Analyses

### 4.4.1. Definition of endpoint

- Change from baseline in Control of Eating Questionnaire (CoEQ) subscale scores and individual responses at Weeks 48 and 96.
    - The CoEQ comprises 19-items that are designed to assess the severity and type of food cravings an individual experiences over the previous 7 days. The CoEQ has been used in clinical trials as a multi-dimensional measure of appetite, craving and mood regulation [Dalton, 2015]. There are 4 subscales from seventeen individual items from the CoEQ: Craving Control (items 9, 10, 11, 12 and 19), Craving for Sweet (items 3, 13, 14 and 15), Craving for Savory (items 4, 16, 17 and 18), and Positive Mood (items 5, 6, 7 and 8). Items 1 and 2 are not under any subscales but are to capture sensations of general appetite. The items are assessed using visual analog scales ranging from 0 (not at all) to 10 (extremely).
- Baseline menopausal symptoms (total score, subscale scores, and individual responses) from Menopause Rating Scale (MRS) health-related quality of life (QoL) questionnaire.
    - The MRS consists of a list of 11 individual items. Each individual item measures the level of symptoms or complaints perceived by the women participants that affect their health-related QoL. The level can range from a score of 0 (no complaints) to a maximum of 4 (extremely severe symptoms). These climacteric symptoms represent the gradual change of a woman's ovarian function during perimenopause before menopause actually arrives. Three subscales are available: Psychological score (sum of items 4 to 7), Physical score (sum of items 1 to 3, plus 11), and Urogenital score (sum of items 8 to 10). The scores are totaled for each subcategory. A grand total score ranks the severity of the symptoms a woman experiences around menopause. The MRS can help determine what a woman's baseline level is before any treatment changes are started.

- Change from baseline in HIV Treatment Satisfaction Questionnaire status version (HIVTSQs) total treatment satisfaction score, subscale scores, and individual responses at Weeks 24 and 96.
    - The HIVTSQ status version (HIVTSQs) assesses participants' satisfaction with their current HIV treatment using 10 individual items. Individual item scores range from 0 ("very dissatisfied", "very poorly controlled", "very inconvenient", "very inflexible", "no, I would definitely not recommend the treatment") to 6 ("very satisfied", "very well controlled", "very convenient", "very flexible", "yes, I would definitely recommend the treatment").
- Change from baseline in HIV Treatment Satisfaction Questionnaire change version (HIVTSQc) total treatment satisfaction score, subscale scores, and individual responses at Week 48.
    - The HIVTSQ change version (HIVTSQc) is assessing the change in participants' satisfaction between their previous and their current treatment within the same group. It consists of 10 individual items. All individual items are rated +3 ("much more satisfied now", "much better controlled now", "much more convenient now", "much more flexible now", "much more likely to recommend the treatment now") to -3 ("much less satisfied now", "much worse controlled now", "much less convenient now", "much less flexible now", "much less likely to recommend for treatment now").
- Change from baseline in bothersome symptoms using the Symptom Distress Module (SDM) at 24, 48 and 96 weeks.
    - The SDM is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment. The SDM questionnaire consists of questions for the presence and bothering level (score) of 20 symptoms. The bothering level for each symptom ranges from 1 (i.e., "It doesn't bother me") to 4 (i.e., "It bothers me a lot"), whereas if the symptom is not present the bothering level is 0 (i.e., "I do not have this symptom"). Total bother score is the sum of all 20 symptoms. It has a range of 0 to 80 and can be further grouped into 9 categories: 0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80. The Symptom Count Score is the unweighted sum of the number of symptoms which are present and ranges from 0 (i.e., no symptom is present) to 20 (i.e., all symptoms are present).
- Change from baseline in health-related quality of life using the WHOQOL-HIV BREF at 24, 48 and 96 weeks.
    - The WHOQOL-HIV BREF is the short form of the WHOQOL-HIV. It has 31 items including two general questions and 29 specific questions explaining six domains of quality of life: "Physical wellbeing", "Psychological health", "Level of Independence", "Social Relationships", "Environmental health", and "Spirituality/Religion/Personal Beliefs". The 31-items are rated on a 5-point Likert scale, where 1 indicates "low, negative perceptions" and 5 indicates "high, positive perceptions." Domain scores are scaled in a positive direction, where higher scores denote "higher quality of life." Some items are not scaled in a positive direction (e.g., Pain and Discomfort, Negative Feelings, Dependence on

Medication, Death and Dying), meaning that for these items, higher scores do not denote higher quality of life.

### 4.4.2. Main analytical approach

All exploratory analyses will be performed on the FAS population, unless otherwise specified. For all summaries on absolute and change from baseline values, absolute values will be summarized for the Baseline and all post-baseline visits, while change values will only be summarized for post-baseline visits.

- CoEQ: n, Mean, SD, Median, Q1, Q3, Minimum and Maximum will be used to summarize absolute and change from baseline values in each subscale score by Baseline, Weeks 48, and 96. In addition, the frequencies and percentages of participants having each individual score by Baseline and Weeks 48 and 96 will be provided.
- MRS: n, Mean, SD, Median, Q1, Q3, Minimum and Maximum will be used to summarize the total score of all 11-items and each subscale (psychological, physical, and urogenital) at Baseline. In addition, the frequencies and percentages of participants having each individual score at Baseline will be provided. All summaries for MRS will be first provided for those with sex at birth recorded as female, intersex or declined to answer.
- HIVTSQs: n, Mean, SD, Median, Q1, Q3, Minimum and Maximum will be used to summarize absolute and change from baseline values in total scores (sum of 10 items) and subscale scores (i.e., General Satisfaction/Clinical & Lifestyle/Ease sub-scores) by Baseline, Weeks 24, and 96. In addition, the frequencies and percentages of participants having each individual score (0 through 6) by Baseline, Weeks 24 and 96 will be provided.
- HIVTSQc: n, Mean, SD, Median, Q1, Q3, Minimum and Maximum will be used to summarize absolute values in total scores (sum of 10 items) and subscale scores (i.e., General Satisfaction/Clinical & Lifestyle/Ease sub-scores) at Week 48. In addition, the number and percent of participants having each individual score (3, 2, 1, 0, -1, -2 and -3) by Week 48 will be provided.
- SDM: n, Mean, SD, Median, Q1, Q3, Minimum and Maximum will be used to summarize absolute and change from baseline values in bothering level score by Baseline, Weeks 24, 48, and 96. The same will also be used to summarize absolute values in symptom count score by Baseline, Weeks 24, 48, and 96. In addition, the frequencies and percentages of participants with each type of symptom and each bother score category by Baseline, Weeks 24, 48, and 96 will be provided in separate summaries.
- WHOQOL-HIV BREF: n, Mean, SD, Median, Q1, Q3, Minimum and Maximum will be used to summarize absolute and change from baseline values in each domain score (physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs) and for question 1 (How would you rate your quality of life?) by Baseline, Weeks 24, 48, and 96. For individual item 1, shift from Baseline categories by visit will be presented using frequencies and percentages.

In addition, the number and percent of participants having each individual score by Baseline, Weeks 24, 48, and 96 will be provided.

**Table 12 Overview of Planned Exploratory Efficacy Analyses**

| Endpoints | Absolute Values/ Frequency and Percentages | | Change from Baseline/ Shift in Category | |
|---|---|---|---|---|
| | Summary | | Summary | |
| | T | F | T | F |
| **Control of Eating Questionnaire (CoEQ)** | | | | |
| Individual CoEQ Scores | Y | | | |
| CoEQ Subscale Scores | Y | | Y | |
| **Menopause Rating Scale (MRS)** | | | | |
| MRS Individual Item Scores at Baseline | Y | | | |
| MRS Total and Subscale Scores at Baseline | Y | | | |
| **HIV Treatment Satisfaction Questionnaires (HIVTSQs and HIVTSQc)** | | | | |
| HIVTSQs Individual Item Scores by Visit | Y | | | |
| HIVTSQs Total and Subscale Scores by Visit | Y | | Y | |
| HIVTSQc Individual Item Scores by Visit | Y | | | |
| HIVTSQc Total and Subscale Scores by Visit | Y | | Y | |
| **Symptom Distress Module (SDM)** | | | | |
| Symptom Count by Visit | Y | | Y | |
| Symptom Bother Score by Visit | Y | | Y | |
| Percent of Participants with Each Symptom | Y | | | |
| Percent of Participants with Each Bother Score Category | Y | | | |
| **World Health Organization Quality of Life (WHOQOL-HIV BREF)** | | | | |
| Individual Item Scores by Visit | Y | | | |
| Domain Scores and Q1 by Visit | Y | | Y | |
| Q1 Shift from Baseline by Visit | | | Y | |

## 4.5. Safety Analyses

The safety analyses will be based on the FAS, unless otherwise specified. No dose adjustments are permitted in this study.

### 4.5.1. Extent of Exposure

The number of days of exposure to study treatment will be calculated based on the formula:

> Overall Duration of Exposure in Days = (Study Treatment Stop Date – Study Treatment Start Date) + 1.

Participants who are enrolled in the study but do not have Study Treatment Start Date will be categorized as having zero days of exposure.

An actual calculation of exposure will be performed where the duration of any dosing interruptions or missed based on eCRF data will be subtracted from the result above.

> Actual Duration of Exposure in Days = [(Study Treatment Stop Date – Study Treatment Start Date) + 1] – (Total Number of Days of Study Treatment Interruption/Missed)

The total number of days of study treatment interruption or missed for a specific visit will be determined as the number of treatment dose returned across all bottles dispensed for the period. All time of study treatment interruptions/missed are summed to get the total number of days of study treatment interruption/missed.

Participants with partial or missing treatment stop dates will be imputed as described in Section 6.3.9.

Overall duration and actual duration of exposure in days will be summarized with n, Mean, SD, Median, Q1, Q3, Minimum, and Maximum. The duration of dosing in participant years will be calculated as the (sum of the actual duration of dosing in days for all exposed participants)/365.25.

A listing of all exposure data will also be produced.

### 4.5.2. Study Treatment Compliance

Compliance data such as total number of treatment doses dispensed and returned is collected in the Drug Accountability page in CRF and will be used to calculate the compliance rate:

> Study Treatment Compliance (%) = [(Total number of treatment doses dispensed – Total number of treatment doses returned)] / Total number of treatment doses dispensed] *100.

Overall compliance rate will include all doses dispensed and returned within the duration of the study.

Additionally, missed dosage will be calculated from the Continual Dosing CRF and summarized by percent of missed doses and by summary statistics for participants who have missed at least one dose.

Missed Dosage (%) = 100*(Total number of days of study treatment interruption / Overall duration of exposure in days) where study treatment interruption is at least one missed dose.

### 4.5.3. Adverse Events

Adverse event analyses including adverse events (AEs), serious adverse events (SAEs) and other significant AEs will be based on PPD/CDISC Data Standards. Adverse events will be coded using the latest version of standard Medical Dictionary for Regulatory Activity (MedDRA dictionary) at the time of database lock before analyses.

AEs will be summarized using frequencies of participants and their percentages. All AE outputs that will be tabulated by System Organ Class (SOC) and Preferred Term (PT), unless indicated otherwise. SOCs will be sorted in descending order of the total incidence then alphabetically, and PTs will be sorted within the SOC in descending order of the total incidence then alphabetically. For AEs captured more than once, the most severe intensity will be included in summaries, and all events will be included in listings. For the purposes of summarizing AE data, unless stated otherwise, the summaries will include post-baseline data (i.e., treatment phase and any follow-up).

For completely missing or partially missing AE start date or end date, imputation rules will be applied following Section 6.3.3. AEs with missing relationship, missing serious indicator, and missing severity will be included in summaries as missing without any imputations.

Table 13 provides an overview of the safety planned analyses.

**Table 13 Overview of Planned Safety Analyses**

| Endpoint | Summary | | Individual | |
|---|---|---|---|---|
| | T | F | F | L |
| **Exposure** | | | | |
| Extent of Exposure | Y | | | Y[1] |
| **Adverse Events[2]** | | | | |
| All AEs by SOC and PT | Y | | | |
| All AEs by SOC, PT and Maximum Grade[2] | Y | | | |
| All Non-Serious AEs | | | | Y[3] |
| Common AEs by Frequency[4] | Y | | | |
| Common Grade 2-5 AEs by Frequency[4] | Y | | | |
| Common Non-Serious AEs by SOC and PT (number of participants and occurrences)[6] | Y | | | |
| Common Drug-Related Grade 2-5 AEs by Frequency[4] | Y | | | |
| All Drug-Related AEs by SOC and PT | Y | | | |
| All Drug-Related AEs by SOC, PT and Maximum Grade[2] | Y | | | |
| Drug-Related Non-Serious AEs by SOC and PT (number of participants and occurrences)[6] | Y | | | |
| Drug-Related AE Leading to Withdrawal from Study | Y | | | |

| Endpoint | Summary | | Individual | |
|---|---|---|---|---|
| | T | F | F | L |
| AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT | Y | | | |
| AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC, PT and Maximum Grade[2] | Y | | | |
| **Serious and Other Significant AEs** | | | | |
| SAEs by SOC and PT (number of participants and occurrences)[6] | Y | | | Y[3] |
| Non-Fatal SAEs | | | | Y |
| All Drug-Related SAEs by SOC and PT | Y | | | |
| All-Cause Mortality | | | | Y |
| Reason for Considering as a Serious Adverse Event | | | | Y |
| **AEs by Subgroup** | | | | |
| All AEs, Grade 2-5 AEs, Drug-Related AEs, Grade 2-5 Drug-Related AEs, SAEs, and AEs Leading to Discontinuation of Study Treatment by Subgroup[5] | Y | | | |

**NOTES :**

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e., descriptive statistics) of the observed raw data.
- Individual = Represents L related to any displays of individual participant observed raw data.

1. Includes reason for any dose change/interruption.
2. For AEs reported more than once by a participant, the most severe intensity will be included.
3. Listing on Non-Serious AEs or Serious AEs will be provided only for participants in Mexico.
4. Common AEs and SAEs are those with >=2% (or >=1% for drug-related grade 2-5 AEs) incidence summarized by frequency.
5. Repeated by maximum grade as well.
6. All AE endpoints will be summarized at any event level only.

#### 4.5.3.1. Adverse Events of Special Interest (AESI)

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting, and/or emerging data from on-going studies may highlight additional adverse events of special interest. Therefore, the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

The following will be considered AESI and each AESI will be summarized:

- Hypersensitivity
- Severe cutaneous adverse reactions
- Depression and suicide/self-injury
- Ischaemic heart disease and cerebrovascular accidents
- Hypertension
- Hyperglycaemia/new onset diabetes mellitus

The terms (e.g. SOC, PT, etc.) necessary to define each AESI will be provided by GSK in a separate document.

An overview of the planned adverse events of special interest analyses are presented in Table 14.

**Table 14 Overview of Planned Adverse Events of Special Interest Analyses**

| Endpoint | Summary | |
|---|---|---|
| | T | F |
| **Adverse Events of Special Interest (AESI)** | | |
| Characteristics of Post-Baseline AESI | Y | |
| Summary of Adverse Events of Special Interest by AESI Category, System Organ Class and Preferred Term (Number of Participants and Occurrences) | Y | |

#### 4.5.3.2. AE Analyses

For completely missing or partially missing AE start date or end date, imputation rules will be applied following Section 6.3.9. AEs with missing relationship, missing serious indicator, and missing severity will be included in summaries as missing without any imputations.

The following AE endpoints at any event level will be summarized by subgroups (see Section 4.6.4 for subgroup's details) using frequencies and percentages in one display:

- All AEs
- Grade 2-5 AEs
- Drug-Related AEs
- Grade 2-5 Drug-Related AEs
- SAEs
- Study drug-related AEs Leading to Discontinuation of Study Treatment

### 4.5.4. Additional Safety Assessments

An overview of the planned additional safety analyses for assessment described from Section 4.5.4.1 to Section 4.5.4.10 is provided in Table 15.

#### 4.5.4.1. Columbia Suicidality Severity Rating Scale

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicidality Severity Rating Scale (eC-SSRS). Results will be analyzed based on the nominal visit.

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. Screening visit questions will be in

relation to lifetime and current experiences (within the past 2 months); all subsequent questioning is about the last assessment. The eC-SSRS will be conducted electronically by telephone or by computer/tablet connected to the internet.

During an assessment, a positive alert is triggered if a participant has reported suicidal ideation/behavior in categories 4-9. Questions in categories 3-5 will be triggered if suicidal ideation is reported in categories 1 or/and 2. Each of the 9 categories capture the following ideation/behavior:

Suicidal Ideation:

- Category 1 – Passive: Wish to be dead
- Category 2 – Active: Non-specific (no method, intention, nor plan)
- Category 3 – Active: With method, but no intention nor plan
- Category 4 – Active: With method and intention, but no plan
- Category 5 – Active: With method, intention, and plan

Suicidal Behavior:

- Category 6 – Preparatory acts or behavior
- Category 7 – Aborted attempt
- Category 8 – Interrupted attempt
- Category 9 – Non-fatal actual suicide attempt

In the case of incomplete calls or duplicate calls, see Section 6.3.3 under eC-SSRS for details on handling approaches.

The following summaries will be produced on suicidal ideation or behavior:

- Summary of True Positive Suicidal Alerts Based on eC-SSRS by Visit using frequencies and percentages.
- Summary of Participants with eC-SSRS Suicidal Ideation or Behavior Pre-Treatment using frequencies and percentages.
- Summary of Participants with Post-Baseline (regardless of visits) eC-SSRS Suicidal Ideation or Behavior using frequencies and percentages.

#### 4.5.4.2. Laboratory Data

Central laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and Liver Function tests will be based on PPD/CDISC Data Standards. Local and retrospective data (with the exception of CD4 nadir) will be excluded from TFL outputs. See in Section 6.3: Appendix 2 Data Derivations Rule for details on missing data handling and laboratory data variables that require data transformation such logs, etc..

In general, all quantitative laboratory data including data from hematology, chemistry, and urinalysis will be summarized with descriptive statistics (n, mean, standard deviation, Q1, median, Q3, minimum, and maximum) at baseline and at each post-baseline visit as indicated in the Schedule of Activities (Section 6.4), including change from baseline for post-baseline visits.

All qualitative laboratory data will be presented as frequencies and percentages at each visit. The percentages will be based on the number of participants with non-missing data at each visit for each laboratory parameter.

Summaries of worst-case(maximum) grade increase from baseline grade will be provided for clinical chemistries, hematology, and fasting lipids with abnormalities of ≥ Grade 1. A similar summary will also be produced for AST, ALT, and Total Bilirubin but further tabulated by baseline Hepatitis C status. All grades will be based on DAIDS. Worst case is defined as the most abnormal result (i.e. the highest of any high results > Upper Limit of Normal (ULN) or the lowest of any low results <Lower Limit of Normal (LLN)) for that parameter. These summaries will display the frequencies and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

An e-DISH plot of maximum post-baseline total bilirubin versus maximum post-baseline ALT will be created. Scatter plots of maximum post-baseline versus baseline will be created for ALT and total bilirubin.

#### 4.5.4.3. Liver Fibrosis

Summaries of absolute and change from baseline values in liver fibroscan measurements including liver stiffness measurement (LSM [kPa]) and CAP score (dB/m) will be summarized using n, mean, standard deviation, Q1, median, Q3, minimum, and maximum by visit at Baseline, Weeks 48 and 96. The same summaries will also include two other calculated fibrosis measurements Fibrosis-4 index and Nonalcoholic Fatty Liver Disease (NAFLD) Fibrosis Score (NFS). Frequencies and percentages for changes in fibrosis score (F0 to F4 based on LSM), Steatosis grade (None, S1-S3 based on CAP score), FIB-4 categories, and NFS categories from baseline categories will be provided at Weeks X. In addition, incidence of F4 (LSM based) among participants without it at baseline will be summarized using frequencies and percentages for post-baseline period. The same summary will also be produced for S3(CAP based), Advanced fibrosis (FIB-4 based), and Advanced fibrosis (NFS based). Calculations on measurements and groupings on their categories are provided in Table 20.

#### 4.5.4.4. Liver Monitoring/Stopping Events

Liver events including participants meeting monitoring criteria and/or stopping criteria are collected from Liver Events Reporting CRF. Summary of Liver Monitoring/Stopping Event Reporting including frequencies and percentages of participants meeting monitoring/stopping criteria, whether event is resolved, and whether any study treatment restart/rechallenge happens after meeting a stopping criterion, will be provided.

#### 4.5.4.5. Lipids

Summaries on absolute, change from baseline, and percent change from baseline fasting lipids (total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, and TC/HDL ratio) will be provided by Baseline, Week 24, Week 48, and Week 96. Summary of changes in NCEP fasting lipid baseline category to Week X category (shift table), to maximum post-baseline category (shift table), and to minimum post-baseline category (shift table) will be provided separately. In addition, a band plot of NCEP categories in fasting lipids overtime will also be provided. All summaries will be repeated to include non-fasting participants and those on lipid-modifying agents.

#### 4.5.4.6. Renal Biomarkers

Summaries of absolute, change from baseline, and percent change from baseline in renal biomarkers [Cystatin C (blood), Retinol Binding Protein (RBP, blood/urine), Beta-2-Microglobulin (B2M, blood/urine), urine beta-2 microglobulin:urine creatinine ratio, urine retinol binding protein4:urine creatinine ratio, and estimated glomerular filtration rate (eGFR; based on Cystatin C CKD-EPI uncorrected for Race)] by Baseline, Weeks 24, 48 and 96 will be provided. Separate summaries will also be provided on the log transformed data.

#### 4.5.4.7. Bone Biomarkers

Summaries of absolute, change from baseline, and percent change from baseline in bone biomarkers (bone specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, and 25 hydroxy-Vitamin D) by Baseline, Weeks 24, 48 and 96 will be provided. Separate summaries will also be provided on the log transformed data.

#### 4.5.4.8. Insulin Resistance

Summaries of absolute and change from baseline in homeostasis model of assessment-insulin resistance (HOMA-IR) at Baseline, Weeks 48 and 96 will be provided. HOMA-IR shift tables (based on cut-offs < 2, 2 to < 3, 3 to < 4, >=4) from baseline to each post-baseline visit will also be provided. Scatter plots of change in HOMA-IR from Baseline vs change in weight from Baseline will be provided by Weeks 24, 48 and 96 along with the Pearson Correlation Coefficient. Participants who are diabetic or who have taken anti-diabetic medication up until or at Baseline are excluded from HOMA-IR analyses. All summaries will be provided for fasting participants and repeated to include non-fasting participants. More details regarding HOMA-IR can be found in Section 6.3.3.

In addition, summaries of absolute and change from baseline at each visit will be provided for the Triglyceride and glucose index (TyG), which is a simple measure of insulin resistance and a predictor of nonalcoholic fatty liver disease (NAFLD). TyG will be calculated as

> TyG = ln[TG (mg/dL) x SG (mg/dL)]/2, where TG = triglycerides and SG = serum glucose.

TyG will also be categorized based on a systematic literature review [Sánchez-García, 2020] as ‘Normal: <4.49’ and ‘Insulin resistance: ≥4.49’. The frequencies and percentages of participants falling into these categories will be summarized at each applicable visit. All TyG summaries will be provided for fasting participants and repeated to include non-fasting participants and those on lipid-modifying agents.

#### 4.5.4.9. Cardiovascular (CV) Risk and CV Events

CV risk will be assessed using the Framingham equation and DAD equation (both equations can estimate 10-year risk for CVD in %, details can be found in Section 6.1.3). Framingham equation takes the following into account when computing the risk: age, sex, systolic blood pressure, antihypertensive therapy, serum TC values, HDL-cholesterol values, diabetes, smoking status. DAD equation takes the following into account when computing the risk: age, sex, systolic blood pressure, serum CT values, HDL-cholesterol values, diabetes, smoking status, family history of CVD, current use of abacavir, indinavir, or lopinavir, and the number of years on indinavir or lopinavir [Nery, 2013].

Summaries of absolute and change from baseline in Framingham and DAD risk scores by Weeks 48 and 96 will be provided. Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

Arrhythmias

Congestive Heart Failure

CVA (Stroke) / Transient Ischemic Attack

Deep Vein Thrombosis/ Pulmonary Embolism

Myocardial Infarction

Peripheral Arterial Thromboembolism

Pulmonary Hypertension

Revascularization

Valvulopathy

#### 4.5.4.10. Vital Signs

Vital signs measurements collected include SBP, DBP, pulse rate (PR). Vital signs will be summarized with descriptive statistics (n, mean, standard deviation, Q1 median, Q3, minimum and maximum) at each visit and the change from baseline to each post-baseline visits. Visits include Baseline, Week 4, Week 12 Week 24, Week 48, Week 72, and Week 96.

Participants with missing baseline values are assumed to have within range baseline values.

For PR, each vital sign result will be classified as Normal (N) when its value is within the lower and upper limit of the vital sign variable; Low (L) when its value is equal or less than the lower limit of the vital sign variable; and High (H), when its value is equal or higher than the upper limit of the vital sign variable.

| Vital Sign Parameter (Absolute) | Units | Potentially Clinically Important Range | |
|---|---|---|---|
| | | Lower | Upper |
| Pulse Rate | bpm | < 40 | > 110 |

For SBP and DBP the following classifications will be defined.

| Classification | SBP (mmHg) | DBP (mmHg) |
|---|---|---|
| Low | <85 | <45 |
| Normal | ≥85 to <130 | ≥45 to <80 |
| Pre-Hypertensive | ≥130 to <140 | ≥80 to <90 |
| Grade 1 | ≥140 to <160 | ≥90 to <100 |
| Grade 2 | ≥160 to <180 | ≥100 to <110 |
| Grade 3 | ≥180 | ≥110 |

The frequencies and percentages of participants falling into any of the categories described above will be summarized at each visit. In addition, shift tables representing the changes from baseline to each post-baseline visit will be presented.

Scatter plots on the following will be provided by Weeks 24, 48 and 96 along with Pearson Correlation Coefficient:

- Change in systolic blood pressure (SBP) from Baseline vs change in weight from Baseline.
- Change in diastolic blood pressure (DBP) from Baseline vs change in weight from Baseline.

#### 4.5.4.11. Electrocardiograph (ECG)

ECG measurements at baseline will be recorded, including pulse rate, PR interval, QRS duration, Uncorrected QT interval, QTcB (Bazett), QTcF (Fridericia), QTc Correction Method Unspecified, QRS Axis and RR interval. Corrected QT intervals will be calculated by Bazett's formula:

$$\text{QTcB (msec)} = \frac{QT}{\sqrt{\text{RR}/1000}}$$

and by Fridericia's formula:

$$\text{QTcF (msec)} = \frac{QT}{\sqrt[3]{RR/1000}}$$

depending on the availability of other measurements.

**Table 15 Overview of Planned Additional Safety Analyses**

| Endpoint | Absolute Values/ Frequency and Percentages | | | | Change from Baseline/ Shift in Category | | | | Max Post BL | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Summary | | Individual | | Summary | | Individual | | Summary | |
| | T | F | F | L | T | F | F | L | T | F |
| **Columbia Suicidality Severity Rating Scale** | | | | | | | | | | |
| True Positive Suicidal Alerts | Y | | | | | | | | | |

| Endpoint | Absolute Values/ Frequency and Percentages | | | | Change from Baseline/ Shift in Category | | | | Max Post BL | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Summary | | Individual | | Summary | | Individual | | Summary | |
| | T | F | F | L | T | F | F | L | T | F |
| Suicidal Ideation or Behavior | Y | | | | Y | | | | | |
| **Laboratory Values** | | | | | | | | | | |
| Clinical Chemistry | Y | | | Y[1] | Y | | | | | |
| Hematology | Y | | | Y[1] | Y | | | | | |
| Urinalysis | Y | | | Y[1] | Y | | | | | |
| Liver Chemistries | | | | | | | | | | Y |
| Liver Fibroscan (Fibrosis Score, Steatosis Grade, FIB-4, NAFLD Fibrosis Score) [7] | Y | | | | Y | | | | | |
| Liver Monitoring/Stopping Events[6] | Y | | | | | | | | | |
| Fasted Lipid (Triglycerides, LDL, HDL and TC and TC/HDL)[2] | Y[4] | | | | Y[4] | | | | | |
| NCEP shifts in lipids at Week X | | | | | Y[4] | Y[3,4] | | | Y[4] | |
| **Emergent Laboratory Toxicities** | | | | | | | | | | |
| Clinical Chemistry | | | | | | | | | Y | |
| Hematology | | | | | | | | | Y | |
| Fasting LDL Cholesterol Abnormalities of Grade 2 or Greater | | | | | | | | | Y | |
| Participants Meeting Post-Baseline Hepatobiliary Abnormality Criteria | Y | | | | | | | | | |
| AST, ALT and Total Bilirubin Maximum Post-Baseline Emergent Toxicity by Baseline Hepatitis C Status | | | | | | | | | Y | |
| **Clinical Laboratory and Biomarkers** | | | | | | | | | | |
| Renal Biomarkers | Y | | | Y | Y | | | | | |
| Bone Biomarkers | Y | | | Y | Y | | | | | |

| Endpoint | Absolute Values/ Frequency and Percentages | | | | Change from Baseline/ Shift in Category | | | | Max Post BL | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Summary | | Individual | | Summary | | Individual | | Summary | |
| | T | F | F | L | T | F | F | L | T | F |
| HOMA-IR by Visit | Y | | | | Y | | | | | |
| Triglycerides and Glucose Index (TyG) by Visit | Y | | | | Y | | | | | |
| HOMA-IR Shift Table Based on Cut-off (< 2, 2 to < 3, 3 to < 4, >=4) | | | | | Y | | | | | |
| HOMA-IR vs Weight Scatter Plot | | | | | | Y[5] | | | | |
| **Cardiovascular Risks** | | | | | | | | | | |
| Framingham and DAD Cardiovascular Risk Scores by Visit | Y | | | | Y | | | | | |
| **Vital Signs** | | | | | | | | | | |
| Vital Signs | Y | | | | Y | | | | Y | |
| SBP vs Weight Scatter Plot | | | | | | | Y[5] | | | |
| DBP vs Weight Scatter Plot | | | | | | | Y[5] | | | |

**NOTES :**

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e., descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual participant observed raw data.

1. Listings for participants with abnormalities for values outsides normal range or for potential clinical importance, defined as any Grade 2-5 toxicity for Chemistry (Including Lipids), and Hematology. For Urinalysis, it will be presented as a separate listing and only participants with abnormalities for potential clinical importance will be included.
2. Present mmol/L.
3. Band plot of NCEP categories in lipids over time.
4. Participants on lipid-lowering agents at baseline are not included in summaries. See Lipids Parameters in Section 6.3.3 for more details.
5. A scatter plot of change from baseline in the first endpoint (y-axis) vs change from baseline in the second endpoint (x-axis) at Weeks 24, 48 and 96.
6. Includes counts and percentage for participants meeting monitoring/stopping criteria, whether event is resolved, and whether any study treatment restart/rechallenge happens after meeting a stopping criterion.
7. Continuous and categorical variables of the fibrosis measurements will be summarized separately.

#### 4.5.4.12. Weight, BMI, Waist Circumference, Hip Circumference, Waist to Height, and Waist to Hip Ratio

Absolute and change from baseline values in weight, BMI, waist circumference, hip circumference, waist to height ratio, and waist to hip ratio will be separately summarized using descriptive statistics (n, mean, standard deviation, Q1 median, Q3, minimum and maximum) by visit at Baseline, Week 24, Week 48, and Week 96.

Two specific cut-off of weight change (both increase and decrease) from baseline will be defined as >5% and >10%. The proportions of participants with change from baseline in weight (>5% and >10%) at Week X will be summarized with frequencies and percentages.

A change from baseline to Week X in BMI's standard four categories as defined in Section 6.1.3 will be summarized with frequencies and percentages.

#### 4.5.4.13. Body Morphology Assessed by Dual-X-Absorptiometry (DXA)

Among the participants who have received DXA scans, absolute and change from baseline values in total and regional (trunk and limbs) fat in % and grams, lean mass in % and grams, and estimated visceral adipose tissue (VAT) volume by DXA will be summarized with descriptive statistics (n, mean, standard deviation, Q1 median, Q3, minimum and maximum) by Baseline, Week 48, and Week 96.

An overview of planned analyses on endpoints described in Section 4.5.4.12 and Section 4.5.4.13 is provided in Table 16.

**Table 16 Overview of Weight, BMI, Waist to Height/Hip Ratio and Body Morphology**

| Endpoint | Absolute Values/ Frequency and Percentages | | | | Change from Baseline/ Shift in Category | |
|---|---|---|---|---|---|---|
| | Summary | | Individual | | Summary | |
| | T | F | F | L | T | F |
| **Weight, BMI, Waist/Hip Circumference, Waist to Height Ratio, and Waist to Hip Ratio** | | | | | | |
| Weight by Visit | Y | | | | Y | |
| BMI (continuous) by Visit | Y | | Y[1] | | Y | |
| Proportion of Participants with Change from Baseline in Weight [>5% and >10%] at Week X | | | | | Y | |
| BMI (categorical) shift Table to Week X [2] | | | | | Y | |
| Waist Circumference, Hip Circumference, Waist to Height Ratio, and Waist to Hip Ratio by Visit [3] | Y | | | | Y | |
| DXA Data by Visit [4] | Y | | | | Y | |

Note: If change in weight is not normally distributed, the data will be log transformed and geometric mean will replace arithmetic mean, a 95% CI will replace the standard deviations.

1. Band plot of BMI categories over time.
2. Shift table based on the following BMI categories adopted by the WHO and FDA: Underweight (BMI of < 18.5 kg/m2); Normal (BMI of 18.5 to 24.99 kg/m2); Overweight (BMI of 25 – 29.99 kg/m2); Obese (BMI of >= 30 kg/m2). Any shift to a higher BMI category counts as a shift to a "worse category".
3. Waist to Height ratio will be calculated as Waist circumference in centimeters (cm) divided by Height (from Day 1) in cm. Waist to Hip ratio will be calculated as Waist in cm divided by Hip in cm.
4. Includes only a subset of participants performing DXA scans.

## 4.6. Other Analyses

### 4.6.1. Substance Use History

A summary of substance use history as collected in CRF will be provided for use of tobacco, alcohol, and recreational drugs by Baseline, Week 24, Week 48, and Week 96.

### 4.6.2. Metabolic Syndrome

Metabolic Syndrome (based on International Diabetes Foundation (IDF) [Zimmet, 2005])

| Metabolic syndrome (required at Baseline and Week X) is defined as a participant having:<br>Central obesity (defined as the last value within the visit window of interest as BMI>=30kg/m2)<br>plus any two of the following four factors: | |
|---|---|
| Raised triglycerides | The last fasted value within visit window of interest >=150 mg/dL (1.7 mmol/L)<br>***or*** specific treatment for this lipid* abnormality at any time prior the end of the visit window of interest |
| Reduced HDL cholesterol | The last fasted value within visit window of interest:<br>< 40 mg/dL (1.03 mmol/L) in males<br>< 50 mg/dL (1.29 mmol/L) in females<br>***or*** specific treatment for this lipid* abnormality at any time prior the end of the visit window of interest |
| Raised blood pressure | Baseline systolic BP ≥ 130 or Baseline diastolic BP ≥ 85 mm Hg<br>***or*** treatment* of previously diagnosed hypertension at any time prior the end of the visit window of interest<br>***or*** any AE with preferred term "Hypertension", "Essential hypertension", "Blood pressure increased" or "Blood pressure diastolic increased" experienced at any time prior to the end of the visit window of interest |
| Raised fasting plasma glucose | The last value within visit window of interest (FPG) >= 100 mg/dL (5.6 mmol/L),<br>***or*** previously diagnosed type 2 diabetes at any time prior the end of the visit window of interest |

The number of participants who have metabolic syndrome will be summarized using frequencies and percentages at Week X.

### 4.6.3. Pregnancy Information

Pregnancy tests will be performed according to the schedule of activities in Appendix 3 in Section 6.4 It will also be performed prior to any DXA scan, and the scan will only be performed after a confirmed negative pregnancy test.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or

SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Participants who become pregnant can elect to remain in study with treatment after a discussion to assess the benefit/risk of continuing in the study is undertaken.

A listing of participants who became pregnant during the course of the study will be provided.

### 4.6.4. Subgroup analyses

The list of subgroups will be used in descriptive summaries. Additional subgroups of clinical interest may also be considered.

- If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to end of the study. Any collapses of subgroup levels due to small sample size will be reviewed prior to implementation to ensure they are clinically meaningful.

## Table 17 Subgroups

| Subgroup Category | Subgroup variables and levels |
|---|---|
| Demographic and Baseline Characteristics | • Age (years)[1]<br>  ○ <65, ≥65<br>• Sex[1]<br>  ○ Female, Male<br>• Race[1]<br>  ○ White, Black or African American, Asian, Other<br>• Sex and Age[1]<br>  ○ Female and <65y, Female and ≥65y, Male and <65y, Male and ≥65y<br>• Sex and Race[1]<br>  ○ Female and White, Female and Black or African American, Female and Asian, Female and Other, Male and White, Male and Black or African American, Male and Asian, Male and Other<br>• Self-Identified Gender[1,2]<br>  ○ Man (Cisgender Man, Transgender Man), Woman (Cisgender Woman, Transgender Woman), Other (Nonbinary, Gender Queer, Decline to Answer)<br>• BMI[1]<br>  ○ Underweight/Normal (<25 kg/m$^2$), Overweight 25 - <30 kg/m$^2$), Obese (≥ 30 kg/m$^2$)<br>• Ethnicity[1]:<br>  ○ Hispanic or Latino, Not Hispanic or Latino<br>• Country[1]<br>  ○ United States, United Kingdom, Austria, France, Belgium, Netherlands, Spain, Italy, Portugal, Canada, Germany, Mexico<br>• Region[1]<br>  ○ North America, Europe<br>• Baseline CD4+ cell count (cells/mm$^3$)<br>  ○ <350, 350 to <500, ≥500<br>• CD4+ Nadir (cells/mm$^3$)<br>  ○ <200, 200 to <350, 350 to <500, ≥500<br>• CDC HIV-1 classification[3]<br>  ○ HIV infection stage 1, HIV infection stage 2, HIV infection stage 3 (AIDS), HIV infection stage unknown |
| Cardiovascular risk | • 10-year Framingham Risk Score for Cardiovascular Disease (%)[1]<br>  ○ <10, 10 to <20, ≥20 |
| Comorbidities at Baseline | • Relevant Comorbidities at Baseline[4]<br>  ○ 0, 1, 2, 3, >3 |
| Comedication (non-ART) | • Use of Comedications[5]<br>  ○ Yes, No<br>  ○ 1, 2 to 3, 4 to 5, >5 |
| Prior ART duration[6] | • ≤ 5 years, >5 years to 10 years, >10 years |

**NOTE:**
[1]See 6.1.3 for additional details on demographic and baseline characteristics.
[2]Summaries will be presented by category and subcategory.
[3]See 6.3.11 for additional details on CDC HIV-1 classification.
[4]Relevant comorbidities include cardiovascular, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders, mental health issues (particularly depression and anxiety disorders), sexual dysfunction and age-related changes such as menopause.
[5]Use of Comedication will be defined as the use of any non-ART medications that has been ongoing for at least 6 weeks prior to Baseline.
[6]Prior ART duration will be calculated using End date – Start date as collected in the Prior Antiretroviral Therapy form in CRF. Partial dates will be imputed as described in Section 6.3.9.

Subgroup analyses for the endpoints will be presented as shown in the table below.

**Table 18 Overview of Planned Subgroup Analyses**

| | Endpoint | | | | | |
|---|---|---|---|---|---|---|
| **Subgroup** | **Study Outcomes (Plasma HIV-1 RNA <50 c/mL and Plasma HIV-1 RNA <20 c/mL)** | **CD4+ Cell Count** | **CD4+/CD8+ Cell Count Ratio** | **Demographic and Baseline Characteristics** | **AEs[1]** | **Health Outcomes[2]** |
| Age (years): <65, ≥65 | Y | Y | Y | Y | Y | Y |
| Sex: Female, Male | Y | Y | Y | Y | Y | Y[3] |
| Race: White, Black or African American, Asian, Other | Y | Y | Y | Y | Y | Y |
| Sex and Age: Female and <65, Female and ≥65, Male and <65, Male and ≥65 | Y | Y | Y | Y | Y | Y[3] |
| Sex and Race: Female and White, Female and Black or African American, Female and Asian, Female and Other, Male and White, Male and Black or African American, Male and Asian, Male and Other | Y | Y | Y | Y | Y | |
| Self-Identified Gender: Man (Cisgender Man, Transgender Man), Woman (Cisgender Woman, Transgender Woman), Other (Nonbinary, Gender Queer, Decline to Answer) | Y | Y | Y | Y | Y | |
| BMI: Underweight/Normal | Y | Y | Y | Y | Y | |

| | Endpoint | | | | | |
|---|---|---|---|---|---|---|
| **Subgroup** | **Study Outcomes (Plasma HIV-1 RNA <50 c/mL and Plasma HIV-1 RNA <20 c/mL)** | **CD4+ Cell Count** | **CD4+/CD8+ Cell Count Ratio** | **Demographic and Baseline Characteristics** | **AEs[1]** | **Health Outcomes[2]** |
| (<25), Overweight (25 - <30), Obese (≥ 30) | | | | | | |
| Ethnicity: Hispanic or Latino, Not Hispanic or Latino | Y | Y | Y | Y | Y | Y |
| Country | Y | Y | Y | Y | Y | |
| Region: North America, Europe | Y | Y | Y | Y | Y | Y |
| Baseline CD4+ cell count (cells/mm$^3$): <350, 350 to <500, ≥500 | Y | Y | Y | Y | Y | |
| CD4+ Nadir (cells/mm$^3$): <200, 200 to <350, 350 to <500, ≥500 | Y | Y | Y | Y | Y | |
| CDC HIV-1 classification: HIV infection stage 1, 2, 3 (AIDS), Unknown | Y | Y | Y | Y | Y | |
| Framingham Risk Score for Cardiovascular Disease (%):<10, 10 to <20, ≥20 | Y | Y | Y | Y | Y | |
| Relevant Comorbidities at Baseline: 0, 1, 2, 3, >3 | Y | Y | Y | Y | Y | Y |
| Use of Comedication: Yes, No | Y | Y | Y | Y | Y | Y |
| Use of Comedication: 1, 2 to 3, 4-5, >5 | Y | Y | Y | Y | Y | Y |
| Prior ART Duration: ≤5 years, >5 years to 10 years, >10 years | Y | Y | Y | Y | Y | |

1. Subgroup analyses will be presented for the following AE endpoints each at any event level: All AEs, Grade 2-5 AEs, Drug-Related AEs, Grade 2-5 Drug-Related AEs, SAEs, and AEs Leading to Discontinuation of Study Treatment.
2. Health outcomes include only calculated scores (total or subscales, whichever applicable) for CoEQ, HIVTSQs, HIVTSQc, MRS(Baseline only), SDM, and WHOQOL-HIV.
3. Subgroups 'Sex' and 'Sex and age' will not be summarized for MRS subgroup tables

## 4.7. Interim Analyses

One IA will be conducted after the last participant evaluable completes the Week 48 visit or prematurely discontinues from the study. The analysis method for the primary efficacy endpoint described in Section 4.2 Primary Endpoints/Estimands Analyses will be used for the IA. Since there is no type 1 error, alpha spending approach is not applicable.

The IA will be conducted such that the ongoing study integrity is maintained.

In addition, adhoc review of data by the iSRC may occur if the review threshold is met. Full details of the analyses to be performed will be provided in the iSRC Charter. These reviews will be conducted on instream data and will not be considered formal study interim analyses.

### 4.7.1. Interim Analysis

The IA will be performed at Week 48 after the completion of the following sequential steps:

- The last participant has completed their visit at Week 48 as defined in the protocol or prematurely discontinues from the study prior to Week 48.
- A soft database lock will be performed: All required database cleaning activities have been completed and, final database release and database freeze have been declared by Data Management.
- All data up to visit at Week 48 will be included for efficacy displays and all available data will be included for safety displays..

### 4.7.2. Final Analysis

The final analysis will be performed after all participants complete 96 weeks (EOS) of follow-up or prematurely discontinue the study. The planned analysis at Week 96 including follow-up visit will be performed after the completion of the following sequential steps:

- Last participant has completed their relevant visit at Week 96 including follow-up visit as defined in the protocol. The analysis for time points will be performed when participants complete visits relevant to that time point i.e., Week 96 including follow-up analysis takes place when the last participant has completed their Week 96 visit including follow-up.
- A hard database lock will be performed: All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management. No additional changes to the database will be allowed after a hard database lock.
- All collected data will be included for data displays in the final analysis.

Further data cuts and analyses may be conducted as necessary in support of regulatory submissions and publications.

## 4.8. Changes to Protocol Defined Analyses

Section 10.13.5.1 of study Protocol Amendment 1 dated 10May2023 indicates that COVID-19 -specific protocol deviations will be captured and analyzed separately. However, a decision by GSK for this SAP is to consider all protocol deviations in one

analysis, without a separate analysis for COVID-19 protocol deviations, due to the end of the COVID-19 pandemic.

# 5. SAMPLE SIZE DETERMINATION

Assuming a 20% screen failure rate, approximately 250 HIV-1 infected adult participants will be screened to achieve approximately 200 enrolled participants. For virological failure (VF), we observed a rate of < 1% in our prior studies, in this more diverse and older study population we assume a VF rate of 1%. Using a two-sided 95% test for one proportion with an estimated sample size of 200, we have 95% confidence that the true population VF rate is no more than 4.2% with 90% power. The estimated two-sided 95% confidence interval using Clopper-Pearson exact methodology assuming a sample size of 200 participants for our assumed VF rate of 1% is 0.1% to 3.6% (width = 3.4%).

Based on our observed virological suppression (VS) rate of 93%, using a two-sided 95% test for one-proportion with an estimated sample size of 200 we have 95% confidence that the true population VS rate is at least 86% with 90% power. The estimated two-sided 95% confidence interval using Wilson (Score) method assuming a sample size of 200 participants for our observed VS rate of 93% is 88.6% to 95.8% (width = 7.2%).

## 5.1. Sample Size Sensitivity for Subgroups

For a sample size of 200 enrolled participants, with a VS rate of 93%, the confidence interval widths for subgroup populations can be estimated using the Wilson-Score method. The study is not powered with respect to these subgroups, hence an estimation approach only is taken. The table below provides estimates of CI widths for the population split of 30% (women, aged 65 and over), 40% (identifying as non-white), 50% (cardiovascular risk > 10%), 60% (white, 1 non-ART concomitant medication), and 70% (men, aged below 65).

**Table 19 Summary of confidence intervals widths for varying subgroup sizes**

| Effect size | Total sample | Subgroup proportion | Subgroup sample | CI of effect | CI width |
|---|---|---|---|---|---|
| VS 93% | 200 | 30% | 60 | (83.64, 97.19) | 13.5 |
| | 200 | 40% | 80 | (85.22, 96.84) | 11.6 |
| | 200 | 50% | 100 | (86.25, 96.57) | 10.3 |
| | 200 | 60% | 120 | (86.98, 96.35) | 9.4 |
| | 200 | 70% | 140 | (87.53, 96.18) | 8.6 |

# 6. SUPPORTING DOCUMENTATION

## 6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Full Analysis Set. A summary of the number of participants in each of the participant level analysis sets will be provided. If the count of participants in the FAS differ from the Enrolled set, the analysis of the study population data may be repeated for the Enrolled Set.

### 6.1.1. Participant Disposition

A summary of participant status and disposition will be provided. This display will show the number and percentage of participants who have completed the scheduled study treatment, are ongoing with study treatment, or have discontinued study treatment prematurely, as well as primary reasons for withdrawal from the study.

A summary of the frequencies and percentages of participants on their screening status and reasons for screen failure will be provided based on the screened analysis set.

A summary of recruitment by country and site using frequencies and percentages will be provided based on the enrolled analysis set.

A summary of the frequencies and percentages of participants' reasons for study withdrawal will be provided. A listing of reasons for study withdrawal will also be provided.

### 6.1.2. Study Populations

A summary of the number and percentage of participants in each analysis population (analysis set, see details in Section 3) will be provided based on the screened analysis set.

A listing of participants in each study population will also be provided.

### 6.1.3. Demographic and Baseline Characteristics

A summary of demographic and baseline characteristics using descriptive statistics will be provided on the information in Table 20 based on the FAS. In addition, a listing of demographic characteristics will be provided.

**Table 20 Demographic and Baseline Characteristics**

Data collected in CRF may contain responses such as Unknown, Declined to Answer, and Not Reported. These responses will be displayed in the summary of the demographic and baseline characteristics only if there are confirmed existing cases.

**Age**

- Age, in whole years, will be calculated with respect to the participant's Screening visit where year of birth is collected.
- The following will be used for calculating age where birth date will be imputed as follows:
  - For all participants, the missing date and month will have this imputed as '30th June'.
  - For analysis purposes, if a participant did not fail to meet inclusion criteria #1 (aged 50 years or older), then set any age imputed as <50 to 50. If the participant failed to meet inclusion criteria #1 then the imputed age will not be reset.
- Year of Birth will be presented in listings as 'YYYY'.
- Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the participant will not be calculated and will remain missing.
- Age will be reported as continuous and additionally with the following age range categories.
  - <65, ≥65

**Sex and Sex Reported at Birth**

- Sex will be reported as collected in CRF
  - Female, Male, Unknown
- Sex reported at birth will be reported as collected in CRF
  - Female, Male, Intersex, Declined to Answer

**Gender**

- Self-identified gender collected in CRF will be treated as sub-categories and grouped into 3 categories. All categories and sub-categories will be reported:
  - Man
    - Cisgender Man, Transgender Man
  - Woman
    - Cisgender Woman, Transgender Woman
  - Other
    - Nonbinary, Gender Queer, Decline to Answer

**Childbearing potential**

- Childbearing potential will be reported as collected in CRF
  - Pre-menarcheal, Post-menopausal, Sterile (of child bearing age), Potentially able to bear children

**Ethnicity**

- Ethnicity will be reported as collected in CRF
  - Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown

**Race**

- The following race information is collected in CRF:
  - American Indican or Alaska Native
  - Asian
    - Asian - Central/South Asian Heritage
    - Asian - East Asian Heritage
    - Asian – Japanese Heritage
    - Asian - South East Asian Heritage
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
    - White - Arabic/North African Heritage
    - White - White/Caucasian/European Heritage
  - Not Reported
  - Unknown
- Race group: 4 main categories will be defined based on information collected in CRF:
  - White comprises White regardless of any sub-heritages.
  - Black or African American comprises Black or African American.
  - Asian comprises Asian regardless of any sub-heritages.
  - Other comprises of American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and participants who selected multiple races.
- The races (with sub-heritages breakdown) as collected in CRF, race combination details if multiple races were selected), and race groups will be summarized.

**Country**

- Country information will be identified from site info. Possible countries include United States, United Kingdom, Austria, France, Belgium, Netherlands, Spain, Italy, Portugal, Canada, Germany, and Mexico

**Region**

- North America comprises United States, Canada, and Mexico
- Europe comprises United Kingdom, Austria, France, Belgium, Netherlands, Spain, Italy, Portugal, and Germany

**Height**

- Height will be summarized in cm as continuous variable

**Weight**

- Weight will be summarized in kg as continuous variable

**BMI**

- BMI is collected as Weight (kg) / Height ($m^2$) in the "Vital signs" page of CRF, using Height at Day 1 for all BMI calculations. Continuous and categorical variables will be summarized.
- BMI classification is based on standard categories adopted by the WHO and FDA:
  - Underweight = BMI of < 18.5 kg/m2
  - Normal = BMI of 18.5 – < 25 kg/m2
  - Overweight = BMI of 25 – < 30 kg/m2
  - Obese = BMI of ≥ 30 kg/m2
- Two BMI classification groupings will be considered:

  Grouping 1:
  - Underweight/Normal = BMI of < 25 kg/m2
  - Overweight = BMI of 25 – <30 kg/m2
  - Obese = BMI of ≥ 30 kg/m2

  Grouping 2:
  - Underweight/Normal = BMI of < 25 kg/m2
  - Overweight/Obese = BMI of ≥ 25 kg/m2

**Waist-to-Hip Ratio**

- Waist-to-Hip Ratio is calculated as Waist(cm)/Hip(cm) and missing data will not be imputed. Both Waist and Hip measurements are collected in CRF's Vital Signs form.

**Liver Fibrosis**

- Categorical Liver fibrosis measurements at baseline will include LSM, CAP score, FIB-4 index and NFS.
- LSM will be collected from fibroscan and will be used as the following fibrosis score classifications:
  - F0 to F1 (Normal) = LSM of 2 to < 7 kPa
  - F2 (Moderate) = LSM of 7 to < 10 kPa
  - F3 (Severe) = LSM of 10 to < 14 kPa
  - F4 (Cirrhosis) = LSM of ≥ 14 kPa
- CAP score will be collected from fibroscan and will be used as the following steatosis grade classifications:
  - None = CAP score of <238 dB/m
  - S1 = CAP score of 238 to < 260 dB/m
  - S2 = CAP score of 260 to < 290 dB/m
  - S3 = CAP score of 290 to 400 dB/m
- FIB-4 index will be calculated as Age [years] x AST levels [U/L])/(Platelet [$10^9$/L] x $ALT^{1/2}$ [U/L] and will use the following classifications:
  - No fibrosis = FIB-4 of < 1.3
  - Indeterminate fibrosis = FIB-4 of 1.3 – < 2.67
  - Advanced fibrosis = FIB-4 of ≥ 2.67
- NFS will be calculated as -1.675 + 0.037 x Age [years] + 0.094 x BMI [kg/$m^2$] + 1.13 x IFG/diabetes [yes = 1, no = 0] + 0.99 x AST/ALT ratio – 0.013 x Platelets [$10^9$/L] – 0.66 x Albumin [g/dL] and will use the following classifications:
  - No fibrosis = NFS of < -1.455
  - Indeterminate fibrosis = NFS of -1.455 – < 0.676
  - Advanced fibrosis = NFS of ≥ 0.676

| Metabolic Syndrome |
| --- |
| • Metabolic syndrome will be classified as:<br>  ○ Yes: defined as the baseline BMI>=30kg/m2 plus any two of the four factors listed in Section 4.6.2.<br>  ○ No: Otherwise<br>• Missing data will not be imputed. |

In addition, the following will also be summarized at Baseline in separate tables to further explore these characteristics:

- Hepatitis Status (Definition details are provided in Section 6.3.3) will be summarized using frequencies and percentages for:
  - Hepatitis B test results (Positive, Negative)
  - Hepatitis C test results (Positive, Negative)
  - Positive Hepatitis B & C test results (B only, C only, B and C, Neither)
- CDC Classification of HIV infection (Details in Section 6.3.11) will be summarized with the following classifications using frequencies and percentages.
  - HIV infection stage 0
  - HIV infection stage 1
  - HIV infection stage 2
  - HIV infection stage 3 (AIDS)
  - HIV infection stage unknown
- Cardiovascular Risk Assessments at screening will be summarized on the following collected data from CRF using frequencies and percentages:
  - Family History of Premature Coronary Artery Disease (Yes, No, Unknown)
  - Tobacco Use Status (Never, Current, Former)
  - History of Angina Pectoris (Yes, No)
  - History of Myocardial Infarction (Yes, No)
  - History of Stroke (Yes, No)
  - History of Diabetes (Yes, No)
  - History of Hypertension (Yes, No)
  - History of Hyperlipidemia (Yes, No)
  - 10-year CVD Risk (%) using Framingham equation (<10, 10 to <20, ≥20) (Details in 6.1.3)
  - 10-year CVD Risk (%) using DAD equation (<10,10 to <20, ≥20) (Details in 6.1.3)

In addition, absolute values on 10-year CVD Risk (%) using Framingham equation and DAD equation will also be summarized using n, Mean, SD, Median, Q1, Q3, Minimum, Maximum. Details on both Framingham and DAD equation are provided in Table 21.

- Distribution of HIV-1 RNA (c/mL) will be summarized with n, Mean, SD, Median, Q1, Q3, Minimum, Maximum, on both absolute values and log10 transformed values. Frequencies and percentages will also be used to summarize the following categories in the same table:
  - <50 c/mL
  - ≥50 c/mL
- Distribution of CD4+ cell counts will be summarized with n, Mean, SD, Median, Q1, Q3, Minimum, Maximum, and for the following categories using frequencies and percentages:
  - <350 cells/$mm^3$
  - 350 to <500 cells/$mm^3$
  - ≥500 cells/$mm^3$

**Table 21 Framingham and DAD Equation for CVD Risks**

**Framingham Equation**

The predicted probability, $\hat{p}$, of having a cardiovascular disease (CVD) within the next 10-years according to the Framingham formula [D'Agostino, 2008] is

For females:

$$\hat{p}_F = 1 - S_0(t)^{\exp\{2.32888 \times \log(age) + 1.20904 \times \log(TC) - 0.70833 \times \log(HDL) + 2.76157 \times \log(SBPu) + 2.82263 \times \log(SBPt) + 0.52873 \times I_s + 0.69154 \times I_d - 26.1931\}},$$

For males:

$$\hat{p}_M = 1 - S_0(t)^{\exp\{3.06117 \times \log(age) + 1.12370 \times \log(TC) - 0.93263 \times \log(HDL) + 1.93303 \times \log(SBPu) + 1.99881 \times \log(SBPt) + 0.65451 \times I_s + 0.57367 \times I_d - 23.9802\}},$$

where

$$S_0(t) = \begin{cases} 0.95012, \text{females} \\ 0.88936, \text{males} \end{cases}$$

*TC* = total serum cholesterol (mg/dL),

*HDL* = serum HDL cholesterol (mg/dL),

*SBPu* = systolic blood pressure (mmHg) if participant is not treated for high blood pressure (note that if a participant is treated for high blood pressure then log(*SBPu*) = 0)

*SBPt* = systolic blood pressure (mmHg) if participant is treated for high blood pressure (note that if a participant is not treated for high blood pressure then log(*SBPt*) = 0)

$$I_s = \begin{cases} 1, \textit{current smoker} \\ 0, \textit{otherwise} \end{cases}$$

$$I_d = \begin{cases} 1, \textit{diabetic} \\ 0, \textit{otherwise} \end{cases}$$

- Total cholesterol and HDL cholesterol are not to be restricted to fasting status and should not exclude participants on lipid-modifying agents.
- A participant will be considered as treated for high blood pressure if the participant has
  - indicated "Yes" to "Has the participant experienced any current or past Medical history condition / event?" in the "Medical History" page of CRF on Screening visit and the condition contains "HYPERTENSION".
  - indicated "Yes" to "Has the participant had Hypertension?" in the "CV Event - Medical Conditions Cardiovascular Risk Factors" page of CRF on Day 1 visit.

If data is not available, then the participant will be considered treated for high blood pressure if the participant receives any medication for hypertension with medication start date on or earlier than risk assessment.

- Smoking status is collected from "Substance Use History" page of CRF on Screening/Day 1 visit as "Never smoked", "Current smoker", "Former smoker". For "Current smoker" it should be set to 1 and for "Never smoked", "Former Smoker" and missing it should be set to 0.
- A participant will be considered as diabetic if the participant has
  - indicated "Yes" to "Has the participant experienced any current or past Medical history condition / event?" in the "Medical History" page of CRF on Screening visit and the condition contains "DIABETES".
  - indicated "Yes" to "Has the participant had Diabetes?" in the "CV Event - Medical Conditions Cardiovascular Risk Factors" page of CRF on Day 1 visit.
  - Baseline (Day 1) fasting glucose ≥ 7.00 mmol/L (126 mg/dL) and HbA1c > 6.5%

If data is not available, the participant will be considered diabetic if they receive any diabetes medication with medication start date on or earlier than risk assessment.

- The 10-year probability of CVD will not be calculated for participants who have
  - indicated "Yes" to "Has the participant experienced any current or past Medical history condition / event?" in the "Medical History" page of CRF on Screening visit and the condition is "MYOCARDIAL INFARCTION".
  - indicated "Yes" to "Has the participant had a Myocardial Infarction?" in the "CV Event - Medical Conditions Cardiovascular Risk Factors" page of CRF on Day 1 visit

These participants will not be included in summary statistics (e.g., mean, SD) of 10-year CVD risk when treating as continuous variable, but will be counted in the highest category of risk (i.e., ≥10%) in the summary by category or as subgroup.

- Framingham Risk will also be calculated at Week 48 and Week 96.
  - Smoking status at Week 48 will be used for Week 48 calculation. Smoking status at Week 96 will be used for Week 96 calculation.
  - Diabetic status is defined as:
    1. Current or past is indicated in the medical conditions eCRF page or CV Event - Medical Conditions Cardiovascular Risk Factors" page of CRF as defined above.
    2. At any time prior to and including the analysis timepoint:
       2a. fasting glucose ≥7.00 mmol/L (126 mg/dL) and HbA1C >6.5%, or
       2b. an adverse event is collected as having "type 1 or type 2 diabetes mellitus"
  - "Treated for high blood pressure" at Week 48 and Week 96 is defined as
    1. hypertension at baseline or
    2. use of medication treating hypertension which started prior to and including the analysis time point

**DAD Equation**

The predicted probability, $\hat{p}$, of having a cardiovascular disease (CVD) within the next 10 years according to the DAD equation [Friis-Møller , 2010] is:

$$\hat{p} = 1 - exp^{(-H*t)}$$

Where

t = amount of time in years where the estimated risk is interested at, e.g. 10 for 10-years estimated risk

H=$exp^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6 x_6+\beta_7 x_7+\beta_8 x_8+\beta_9 x_9+\beta_{10} x_{10}+\beta_{11} x_{11}+\beta_{12} x_{12}}$

The values of β and x are summarized below:

| | CVD model | Covariate, x |
|---|---|---|
| β0 | -10.970 | |
| β1 | 0.041 | β value multiply by duration of indinavir in years |
| β2 | 0.077 | β value multiply by duration of lopinavir in years |
| β3 | 0.489 | β value if receiving abacavir, 0 otherwise |
| β4 | 0.530 | β value if male, 0 if female |
| β5 | 0.348 | β value times (age + t/2)/5 |
| β6 | 0.361 | β value if family CVD history, 0 otherwise |
| β7 | 0.854 | β value if current smoker, 0 otherwise |
| β8 | 0.238 | β value if ex-smoker, 0 otherwise |
| β9 | 0.652 | β value if diabetes, 0 otherwise |
| β10 | 0.195 | β value multiply by cholesterol (mmol/l) |
| β11 | -0.402 | β value multiply by HDL (mmol/l) |
| β12 | 0.054 | β value multiply by (systolic blood pressure)/10 |

For indinavir and lopinavir, if continuing in use, add t/2 years to the duration of use.

### 6.1.4. Current and Past Medical Conditions

Current and past medical conditions are collected in CRF's Medical History form at screening. Current medical conditions will be those events where the status at screening is recorded as "Ongoing at Screening" in CRF. Past medical conditions will be those events where the status at screening is recorded as "Resolved before Screening" in CRF. Summaries of current and past medical conditions will be summarized using frequencies and percentages.

### 6.1.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHODrug Global dictionary. The most recent dictionary version at the time of each data cut and/data lock would be used for each reporting effort. The summary of concomitant medications will be provided by combination term ATC Level 1.

Concomitant medications include any medication taken during the on-intervention period as defined in Section 6.10 of the protocol. Prior medications are all medications taken before the start date of the on-treatment period. Thus, a medication can be considered both prior and concomitant depending on the start and end dates relative to the start date of the on-treatment period.

### 6.1.6. Concomitant Antiretroviral Therapy and Post Study Antiretroviral Therapy

Concomitant and Post Study Antiretroviral Therapies will be coded using the WHODrug Global dictionary. The most recent dictionary version at the time of each data cut and/data lock would be used for each reporting effort.

ART medications will also be classified as prior to screening, concomitant to screening and/or post-treatment according with the following modifications:

- ART starting on or after study treatment stop date will be considered as only post-treatment and not concomitant. It is expected that after discontinuation of study treatment, a participant may immediately begin taking another ART.
- ART stopping on study treatment start date will only be considered as prior and not concomitant.
- Any ART entered on the Prior ART eCRF with partial end date will be assumed to have finished before Day 1.
- ART stopped prior to Day 1 includes all ART that has stopped prior to Day 1. All ingredients from any regimen that is switched to another regimen prior to the screening visit e.g., from TDF-based to TAF-based ART will be presented as having stopped.
- ART Medications received at or after Day 1 while still on study treatment includes all ART that started after Day 1 and before study treatment discontinuation. Note this will be recorded as ConART.
- ART Medications Received at Screening includes all ART that is ongoing at the screening visit only.

Data will be summarized using frequency counts and percentages by WHO drug term for these endpoints: ART stopped prior to Day 1, ART starting after Day 1, and ART starting after Treatment Discontinuation. Time Since First Antiretroviral Therapy until Baseline will also be summarized using n, Mean, SD, Median, Q1, Q3, Minimum and Maximum. Prior ART duration will be calculated using End date – Start date as collected in the Prior Antiretroviral Therapy form in CRF. Partial dates will be imputed as described in Section 6.3.9.

| | Pre-treatment | On-treatment | | | Post-treatment | | Prior | Concomitant | Post |
|---|---|---|---|---|---|---|---|---|---|
| (a) | x————x | | | | | | Y | N | N |
| (b) | x———— | | ————x | | | | Y | Y | N |
| (c) | x———— | | ———— | | | ————x | Y | Y | Y |
| (d) | | | x————x | | | | N | Y | N |
| (e) | | IP Start Date | x———— | IP Stop Date | IP Stop Date+1 | ————x | N | Y | Y |
| (f) | | | | | | x————x | N | N | Y |
| (g) | ?————x | | | | | | Y | N | N |
| (h) | ?———— | | ————x | | | | Y* | Y | N |
| (i) | ?———— | | ———— | | | ————x | Y* | Y* | Y |
| (j) | x———— | | ———— | | | ————? | Y | Y** | Y** |
| (k) | | | x———— | | | ————? | N | Y | Y** |
| (l) | | | | | | x————? | N | N | Y |
| (m) | ?———— | | ———— | | | ————? | Y*** | Y*** | Y*** |
| (n) | x———— | x | | | | | Y | Y | N |
| (o) | ?———— | x | | | | | Y* | Y | N |
| (p) | | x | ————x | | | | N | Y | N |
| (q) | | x | ———— | x | | | N | Y | N |
| (r) | | | | x | — | ————x | N | Y | Y |
| (s) | | | | x | — | ————? | N | Y | Y** |
| (t) | | | | | x | ————x | N | N | Y |
| (u) | | | | | x | ————? | N | N | Y |
| (v) | | | x———— | — | x | | N | Y | Y |

x = start/stop date of medication

? = missing start/stop date of medication

* If a medication is stopped on-treatment or post-treatment and no start date is recorded it will be assumed that the medication was ongoing from the Pre-treatment phase

** If a medication is started Pre-treatment or on-treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study

*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the Pre-treatment phase to the post-treatment phase

## 6.1.7. Protocol Deviations

| Term | Definition |
|---|---|
| **Study Deviation Rules Document** | The document describing study deviations (and associated coding/naming conventions) that may be identified during a study and the frequency of study deviation reviews. |
| **Study Deviation** | The term used to indicate a significant or a non-significant deviation to the protocol or to ICH GCP E6(R2), or non-compliance with applicable regulatory requirements. |
| **Significant Protocol Deviation** | For the purposes of PPD SOP, a significant protocol deviation that affects primary efficacy and safety assessments (as applicable), the safety, or the scientific value of the trial project.<br>ICH E3 Q&A R1 defines a protocol deviation (PD) as “any change, divergence, or departure from the study design or procedures defined in the protocol.”<br>The ICH guidelines also introduce a definition for “important” protocol deviations, defining them as “a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject’s rights, safety, or well-being.” |

| Term | Definition |
|---|---|
| | The PPD CTMS system uses the term "Significant Protocol Deviation" to document the "important" protocol Deviations.<br><br>In the GSK-ViiV Eyewitness study no 'per-protocol' analysis will be performed for this study.<br>This is the reason why in this study there is no need to identify what ViiV SOP classifies as 'significant' deviations.<br><br>This study will identify the 'important' deviations as per ICH-GCP, and document them as "significant" in the PPD CTMS system. The list of "significant protocol deviations" will be summarised in the CSRs and transferred in the SDTM datasets. |
| **Non-Significant Protocol Deviation** | A non-important protocol deviation that is identified but does not impact the end points (as applicable) or the scientific value of the project and does not impact a subject's rights, safety, or well-being. |

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Deviation Rule Document. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorized in the protocol deviations dataset.

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management, participant assessment) will be summarized and listed.

All available data at analysis will be summarized.

## 6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

### 6.2.1. Study Level Compliance

Overall eCOA compliance will be calculated across eC-SSRS, CoEQ, MRS, HIVTSQs, HIVTSQc, SDM and WHOQOL-HIV BREF for all participants for all visits at baseline and after.

The overall compliance will be calculated as:

$$100 \times \left( \frac{Total\ number\ of\ complete\ eCOAs}{Expected\ number\ of\ complete\ eCOAs\ *} \right)$$

*The Expected number of complete eCOA assessments is calculated as the number of assessments each participant is expected to complete whilst they are participating in the study summated across all participants.

An eCOA is considered complete if the eCOA has no missing data or if the missing data can be imputed and is used in the study displays. The eCOAs are expected while the

participant is enrolled in the study (i.e., planned eCOAs that occur after the participant withdraws from the study do not contribute to the expected number of eCOAs).

The target compliance for the study is 70%. The study eCOA compliance will be reported for each treatment group.

### 6.2.2. Endpoint Level Compliance

Endpoint level compliance will be tracked for all the endpoints that contribute to overall eCOA compliance.

- For example, eC-SSRS compliance will be calculated as:

$$100 \times \left(\frac{Total\ number\ of\ complete\ eCSSRS}{Expected\ number\ of\ complete\ eCSSRS}\right)$$

In the event of a participant withdrawing from the study the expected number of eC-SSRS will be reduced accordingly. Other endpoint level compliance will be calculated using the same formula.

| eCOA Endpoint | Visits Assessed | Target Compliance |
|---|---|---|
| Study Level Overall | Screening, Day 1, Week 4, Week 8, Week 12, Week 24, Week 48, Week 84, Week 96, Withdrawal | 70% |
| Clinical eCOA: | | |
| Overall | | 70% |
| eC-SSRS | Screening, Day 1, Week 8, Week 24, Week 48, Withdrawal | 70% |
| CoEQ | Day 1, Week 4, Week12 Week 48, Week 96 | 70% |
| MRS | Day 1 | 70% |
| HIVTSQs | Day 1, Week 24, Week 96, Withdrawal | 70% |
| HIVTSQc | Week 48 | 70% |
| SDM | Day 1, Week 24, Week 48, Week 96, Withdrawal | 70% |

| eCOA Endpoint | Visits Assessed | Target Compliance |
|---|---|---|
| WHOQOL-HIV BREF | Day 1, Week 24, Week 48, Week 96, Withdrawal | 70% |

## 6.3. Appendix 3 Data Derivations Rule

### 6.3.1. General

| **Multiple Measurements at One Time Point** |
|---|
| See Section 6.3.8 |
| **Study Day** |
| See Section 6.3.6 |
| **Post-baseline** |
| Post-baseline refers to the combined time periods of on-treatment and post-treatment. |
| **Study Drug** |
| Study Drug refers to Investigational Product DTG/3TC |

### 6.3.2. Efficacy

**HIV-1 RNA**

**Snapshot**

- It is intended to be primarily a virologic assessment of the endpoint, and as such follows a "virology first" hierarchy.
- Plasma HIV1-RNA < 50 c/mL or plasma HIV1-RNA ≥ 50 c/mL within an analysis window is typically determined by the last available plasma HIV-1 RNA measurement in that window while the participant is on-treatment.
- When no HIV-1 RNA data is available within a window, a participant cannot be classified under HIV1-RNA < 50 c/mL. Depending on the reason for lack of data, the participant will be classified as a HIV1-RNA ≥ 50 c/mL or reported as 'No Virologic Data at Week X'; in the latter case, the algorithm further classifies the nature of the missing data. Typically, a participant withdrawn (i) due to AE or, (ii) for another reason yet was suppressed at the time, will be counted as 'No Virologic Data at Week X'. Should a participant withdraw for reasons other than AE and was not suppressed at the time, they will be a HIV1-RNA ≥ 50 c/mL.
- For each scheduled assessment time, the snapshot response rate for a given threshold (e.g., <50 c/mL) is defined as:

$$\text{Snapshot Rate} = \frac{\text{Number of responders in that analysis window}}{\text{Number of participants in the analysis population}}$$

- Full details of the algorithm, including the handling of special cases, are included in Section 6.5. The date at which the participant 'discontinue/withdrawn from the study' in the Snapshot algorithm is the date of treatment discontinuation, rather than the date of study withdrawal,

**Plasma HIV-1 RNA**

- For summaries and analyses which use HIV-1 RNA level as a continuous measure, the logarithm to base 10 of the value will be used.
- HIV-1 RNA results may be provided as censored values, such as <20 or >9,999,999 c/mL. For the purposes of summary statistics, such values will be replaced by the next value beyond the limit of detection, e.g., 19 or 10,000,000 c/mL, respectively, for the given examples. Data listings will show the censored values as provided.
- Qualitive measures (i.e. "target detected" and "target non-detected") may also be provided by the laboratory vendor for values <20 c/ml. When a measurement of plasma HIV-1 RNA is below the limit of quantification (i.e., 20 c/mL) and is qualitatively observable that will be denoted as a "Target Detected" measure, while HIV-1 RNA below the limit of quantification that is not qualitatively observable that will be denoted as "Target Not Detected". Any measurements <20 c/mL characterized as "Target Non-Detected" or "Target Detected" will be captured in the database.

**Confirmed Virologic Withdrawal (CVW), Suspected Virologic Withdrawal (SVW) and Precautionary Virologic Withdrawal (PVW) and potential Precautionary Virologic Withdrawal (pPVW)**

Please refer to the protocol, Section 7.1.2 for more details of the derivation of CVW, PVW, pPVW and SVWs.

PVW (leading to discontinuation)

- May be met after two consecutive assessments with HIV-1 RNA >=50 and <200 c/mL without an identifiable, non-virologic cause (immunization, illness, nonadherence) and after discussion with Medical Monitor, OR
- Will be met with three consecutive on treatment assessments with HIV-1 RNA >=50 and <200 c/mL

pPVW

- Will be met after two consecutive assessments with HIV-1 RNA >=50 and <200 c/mL. The current HIV-1 RNA values must be below 200 c/mL, but the previous HIV-1 RNA can also have been >=200 c/mL

SVW

- One assessment with HIV-1 RNA >= 200 c/mL after Day 1.

CVW

- Two consecutive assessments with HIV-1 RNA ≥200 c/mL after Day 1.

**General Considerations**

- The subsequent HIV-1 RNA sample taken after SVW will be used for the determination of CVW.
- Based on the protocol specific conditions outlined in the protocol, derivation of SVW and CVW will use nominal visits and unscheduled visits.
- Visit windowing will not be applied.
- The condition of 2-4 weeks between the suspected and confirmatory re-test (as described in protocol Section 7.1.2.1) will not be used when programmatically identifying CVW.
- A participant can only be classified as CVW for the analyses if the participant has not withdrawn IP at the time of the HIV-RNA re-test value (at CVW value), where Treatment Start < HIV-1 RNA sample date <= Treatment Stop Date + 1 (if Treatment Stop date exists). Note: study drug interruptions will not be taken into account when programmatically identifying CVW.
- Similarly, viral loads above criteria cut-offs resulting in SVW, CVW, PVW and pPVW need to have occurred post-Day 1 in order for the criteria to be met. For example an SVW can occur at Week 4 if Week 4 HIV-1 RNA >=200 i.e. the viral load above SVW criterion occurred post-Day 1.
- Additional guidelines specified in the protocol related to participant management only and will not be taken into account when programmatically identifying CVW.
- The SVW can become a pPVW, and then later a PVW, if the confirmatory viral loads are between 50 and 200 c/mL
- Please refer to Section 7.1.2 of the protocol for details of the derivation.

**CDC HIV-1 Classification and HIV-associated conditions**

- HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see 6.3.11).
- Any 'other' conditions reported in the eCRFs will be identified programmatically before being sent for clinical review to determine whether they should be classed as stage 3 associated conditions. Review will be ongoing and as a minimum will take place prior to each reporting effort.

## 6.3.3. Safety

**Laboratory Parameters**

**Lower limit of quantitation**

- Additional non-protocol specified laboratory assessments performed at the institution's local laboratory that are databased will not be included in the listings or analyses/summaries. All analyses will be based on central laboratory assessments only. If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

  Example 1: 2 Decimal places = '< x' becomes x – 0.01
  Example 2: 1 Decimal place = '> x' becomes x + 0.1
  Example 3: 0 Decimal places = '< x' becomes x – 1

**Lab Toxicities – DAIDS Grading**

- Toxicities will be based on the Division of AIDS (DAIDS) grading system, as specified in the protocol.
- Toxicity grades provided by the central laboratory do not distinguish between abnormally high or low criteria, when both are relevant for a particular parameter.
- When summarising toxicity grades for such parameters, they will be categorised as to whether they are above or below the midpoint of normal range.

| Parameter | Below Midpoint | Above Midpoint |
|---|---|---|
| Calcium | Hypocalcaemia | Hypercalcaemia |
| Fasted glucose | Hypoglycaemia | Hyperglycaemia |
| Sodium | Hyponatremia | Hypernatremia |
| Potassium | Hypokalemia | Hyperkalemia |

**Lipid Parameters**

- Participants who initiated serum lipid-lowering therapy at baseline (see Lipid-Modifying Agents below) will be excluded from the analysis.
- All values after initiation of lipid-lowering agents will be set to missing
- Missing scheduled visits do not need to be created
- Lipid analyses will be presented on fasting labs, and then repeated to include non-fasting labs and participants on lipid-modifying agents

**Lipid-Modifying Agents**

- The following ATC codes correspond to lipid-modifying agents:

  ATC Level 2: C10
  ATC Level 3: C10A, C10B (if Level 2 is not available)
  ATC Level 4: C10AA, C10AB, C10AC, C10AD, C10AX, C10AW, C10BA, C10BX (if level 2, 3 are not available)
- Participants are considered to have used a lipid modifying agent at baseline if they were taking the medication at the time of their baseline laboratory assessment or if they stopped their lipid modifying medication within 12 weeks of their baseline lipid testing date.

**National Cholesterol Education Program (NCEP) Lipids Categories**

- In addition to DAIDS toxicity scales (see protocol), lipid values will be categorized according to the 2001 NCEP Adult Lipid Guidelines [Grundy , 2001].

| Parameter | Value Range (mmol/L) | Value Range (mg/dL) | Category |
|---|---|---|---|
| Triglycerides | <1.70 | <150 | Normal |
| | 1.70 to <2.26 | 150 to <200 | Borderline High |
| | 2.26 to <5.65 | 200 to <500 | High |
| | ≥5.65 | ≥500 | Very High |
| Total Cholesterol | <5.18 | <200 | Desirable |
| | 5.18 to <6.21 | 200 to <240 | Borderline High |
| | ≥6.21 | ≥240 | High |
| HDL Cholesterol | <1.04 | <40 | Low |
| | 1.04 to <1.56 | 40 to <60 | Normal |
| | ≥1.56 | ≥60 | High |
| LDL Cholesterol | <2.59 | <100 | Optimal |
| | 2.59 to <3.37 | 100 to <130 | Near/Above Optimal |
| | 3.37 to <4.14 | 130 to <160 | Borderline High |
| | 4.14 to <4.92 | 160 to <190 | High |
| | ≥4.92 | ≥190 | Very High |

**Total Cholesterol / HDL Cholesterol Ratio**

- When both total cholesterol and HDL cholesterol results are available from the same date for a participant, then the ratio will be calculated by dividing the total cholesterol result by the HDL cholesterol result. The ratio can be classified as follows:

| Parameter | Value Range |
|---|---|
| Total Cholesterol / HDL Ratio | < 3.5 |
| | 3.5 to < 4.4 |
| | 4.4 to < 5 |
| | ≥ 5 |

**Glomerular Filtration Rate (GFR)**

- Glomerular filtration rate (GFR) will be estimated by the central laboratory using the refitted, race-neutral Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIcr_R) method [Delgado,2022].

**Refitted, race-neutral CKD-EPIcr_R method equation:**

$$\mathbf{eGFR_{cr} = 142 \times \min(SCr/k,1)^{\alpha} \times \max(SCr/k,1)^{-1.200} \times 0.9938^{age} \times 1.012 \text{ [if female]}}$$

where SCr is standardized serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of SCr/k or 1, max indicates the maximum of SCr/k or 1.

where age (in years) is at time of assessment, κ = 0.7 if female or 0.9 if male, α = -0.329 if female and -0.411 if male, min() indicates the minimum of CRT/κ or 1, max() indicates the maximum of CRT/κ or 1, and CRTmg/dL is serum creatinine concentration in mg/dL. The serum creatinine concentration in mg/dL is obtained from GSK standard units of μmol/L as CRTmg/dL =0.0113x CRTμmol/L.

**CKD-EPI Refitted, race-neutral CKD-EPI-cystatin C equation (2022):** GFR will be estimated by the central laboratory using the refitted, race-neutral CKD-EPI-cystatin C [Delgado, 2022] at day 1, week 48, week 96 and when indicated by renal toxicity criteria

**eGFR = 133 x min(Scys/0.8, 1)-0.499 x max (Scys/0.8, 1)-1.328 x 0.996Age x 0.932 [if female]**

Abbreviations / Units

| |
|---|
| eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2<br>Scys (standardized serum cystatin C) = mg/l<br>min = indicates the minimum of Scys/0.8 or 1<br>max = indicates the maximum of Scys/0.8 or 1<br>age = years |
| **HbA1c** |
| • Missing data will not be imputed. |
| **Bone Biomarkers** |
| • Missing data will not be imputed. |
| **Renal Biomarkers** |
| • Missing data will not be imputed. |
| **Hepatitis Status** |
| • Hepatitis C status will be determined using antibody (IgM or IgG) and/or hepatitis C virus (HCV) RNA assessments performed during screening.<br>• If both antibody and virus RNA assessments are available, then the latter will take precedence and positive/negative status will be based on whether HCV RNA is detectable (i.e., ≥43 IU/mL [≥1.63 log IU/mL]) or not<br>• Antibody (IgM or IgG) status with 'BORDERLINE' or 'REACTIVE' will be considered Positive<br>• A participant will be considered positive for hepatitis B virus (HBV) if they have a positive surface antigen or detectable HBV DNA result during screening. Participants positive for HBV are not allowed to enter the study. |
| **Other Safety Endpoints** |
| **Columbia Suicide Severity Rating Scale (eC-SSRS)** |
| • Missing data will not have any imputation performed.<br>• A positive alert is triggered if a participant has reported suicidal ideation/behaviour in categories 4-9.<br>• Questions in categories 3-5 will be triggered if suicidal ideation is reported in categories 1 or/and 2.<br>• Incomplete calls:<br>o when no complete call is databased on the same day, the data from latest complete call within the visit window will be used<br>o if a participant has only an incomplete call, and it resulted in a positive alert, the relevant pages in the eCRF should be completed, even though the call was incomplete<br>o when a complete call is databased on the same day, the data from the complete call will be used in the summaries.<br>• Duplicate calls, if they occur on the same day:<br>o For summary tables, the entry with latest time record will be used.<br>o For summary tables at baseline, unscheduled repeat visits will not be summarized.<br>o Relevant eCRF pages will be completed based on the latest entry (if it was a positive alert). |
| **Homeostatic model assessment-Insulin Resistance (HOMA-IR)** |
| • HOMA-IR = (plasma insulin (mU/L) * plasma glucose (mmol/L)) / 22.5.<br>• HOMA-IR categories will be categorised as follows:<br>o <2<br>o 2 to <3<br>o 3 to <4<br>o >=4<br>HOMA-IR analyses will be based on fasting values and then repeated to include non-fasted labs. Only participants with post-baseline values will be included in analyses (i.e. participants with missing post-baseline HOMA-IR will not be included in summary tables or figures) and missing data will not be imputed. Additionally, participants who are diabetic as captured on the medical history form at Baseline will be excluded from all HOMA-IR analyses. Finally, any participant who has taken an anti-diabetic medication (ATC code "A10" (**DRUGS USED IN DIABETES))** as captured on the medical history form up to Baseline will be removed from the analysis. |

### 6.3.4. Criteria for Potential Clinical Importance

The Division of AIDS (DAIDS) grading for severity of laboratory toxicities and clinical adverse events is included in the protocol. Labs will be graded automatically by the central lab according to the DAIDS toxicity scales. Reference ranges for all laboratory

parameters collected throughout the study are provided by the laboratory. A laboratory value outside the reference range is considered high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

### 6.3.5. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study treatment period.

For Laboratory, HIV Associated Conditions, Vital Signs, Health Outcomes and Genotypic and Phenotypic Data:

| Treatment Period | Definition |
|---|---|
| Pre-Treatment | Date ≤ Study Treatment Start Date |
| On-Treatment | Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 1 |
| Post-Treatment | Date > Study Treatment Stop Date +1 |

**NOTES:**

- If the study treatment stop date is missing then the assessment will be considered to be On-Treatment

For AE:

| Treatment Period | Definition |
|---|---|
| Pre-Treatment | AE Start Date < Study Treatment Start Date |
| On-Treatment | If AE onset date is on or after treatment start date & on or before treatment stop date.<br>Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date |
| Post-Treatment | If AE onset date is after the treatment stop date.<br>AE Start Date > Study Treatment Stop Date |
| Onset Time Since 1st Dose (Days) | If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date<br>If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1<br>Missing otherwise. |
| Duration (Days) | AE Resolution Date – AE Onset Date + 1 |

**NOTES:**

- Partial AE start date will use imputation as described in Section 6.3.9.
- In the case of a completely missing start date, the event will be considered to have started On-treatment unless an end date for the AE is provided which is before start of study treatment; in such a case the AE is assigned as Pre-treatment.
- If the Study Treatment Stop Date is missing, then any event with a start date on or after Study Treatment Start Date will be considered to be On-treatment.
- If the start date of the AE is after Study Treatment Stop Date but has been recorded as potentially related to study treatment, then it will be classified as On-treatment.

### 6.3.6. Study Day and Reference Date

Reference date is the study treatment start date and will be used to calculate study day for safety measures, efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

### 6.3.7. Assessment Window

Snapshot algorithm, laboratory data, vital signs and genotypic and phenotypic data will be assigned to assessment windows according to actual dates rather than the nominal visit labels as recorded on the eCRF or in the laboratory database. Health outcomes and eC-SSRS will be assigned to assessment windows using the nominal visit labels as recorded on the eCRF.

A window around a target Study Day will typically include all days from the midpoints between it and the target Study Days of the previous and the proceeding visits. In general, the nominal target study day for week w is (7*w)+1.

For data summaries by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a target visit based on the visit window defined in the table below. If all assessments within the same window are from unscheduled visits, the one closest to the target scheduled visit will be taken in the slotting.

For assessments that define screening window, the window will be defined as up to and including day -4.

For Health Outcomes assessments, the window will be defined as the nominal visit date + 14 days. For eC-SSRS assessments specifically, the nominal visits will be used, without window.

## Table 22 Analysis Windows

| Analysis Set / Domain | Parameter (If applicable) | Target Study Day | Analysis Window | | Analysis Timepoint (Nominal Visit) |
|---|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint | |
| Efficacy | Snapshot | | | | |
| | | Day 1 | ≤-28 | Day 1 | Baseline |
| | | Day 29 | Day 2 | Day 56 | Week 4 |
| | | Day 85 | Day 57 | Day 126 | Week 12 |
| | | Day 169 | Day 127 | Day 210 | Week 24 |
| | | Day 337 | Day 295 | Day 378 | Week 48 |
| | | Day 505 | Day 463 | Day 546 | Week 72 |
| | | Day 673 | Day 631 | Day 714 | Week 96 |
| All except Snapshot and Additional Safety endpoints [1] | All except Snapshot, DXA Scan and Liver Fibroscan | | | | |
| | | -28 | ≤-4 | ≤-4 | Screening |
| | | Day 1 | Day -3 | Day 1 | Day 1 |
| | | Day 29 | Day 2 | Day 56 | Week 4 |
| | | Day 85 | Day 57 | Day 126 | Week 12 |
| | | Day 169 | Day 127 | Day 252 | Week 24 |
| | | Day 337 | Day 253 | Day 420 | Week 48 |
| | | Day 505 | Day 421 | Day 588 | Week 72 |
| | | Day 673 | Day 589 | Day 714 | Week 96 |
| | | Study Day closest to treatment discontinuation + 1 | > Study Day of treatment discontinuation +1 | > Study Day of treatment discontinuation +1 | Follow-up [2] |
| | | | | | |
| Additional Safety endpoints | DXA Scan for Body Composition and Liver Fibroscan | | | | |
| | | Day 1 | Day -3 | Day 42 | Day 1 |
| | | Day 337 | Day 331 | Day 378 | Week 48 |
| | | Day 673 | Day 667 | Day 714 | Week 96 |

[1] Excludes health outcome analyses.
[2] Analysis visit windowing for follow-up data should not be implemented for disposition, exposure and compliance analyses.

For data summaries by visit, scheduled visits with nominal visit description as shown under the Analysis Timepoint in Table 22 and the worst-case post-baseline (for laboratory summaries) will be shown.

All unscheduled visits will be displayed in any listings, as appropriate.

### 6.3.8. Multiple Measurements at One Analysis Time Point

- If there are multiple assessments within the Screening window, the last assessment through Day -4 will be used.
- If there are multiple assessments within the Day 1 window, the latest pre-dose assessment will be used.
- Otherwise, and with the exception of the Snapshot endpoints, if after window assignment (see 6.3.7), there are multiple valid assessments of a parameter within the same window, then the following hierarchy will be used to determine the value to be used for summary statistics of observed values:
    - the assessment closest to the window target Study Day;
        - if there are multiple assessments equidistant from the target Study Day, then for continuous variables the mean of these values will be used and for categorical variables the worst assessment will be used. For HIV-1 RNA, if there is more than one result on the same day, the result used for decision-making at site should be used. For HOMA-IR and biomarkers data which has been log transformed, the geometric mean will be used when averaging two records equidistant from the target study day.
- Assessments not chosen for use in summary statistics by this algorithm will still appear in the associated listings. Also, such valid assessments will be used when determining values of potential clinical concern for the 'any time on-treatment' time point, and for any algorithm that has specific rules for which observation to use (e.g., SNAPSHOT).

### 6.3.9. Handling of Missing and Partial Dates

**Table 23 Handling of Missing and Partial Dates**

| Element | Reporting Detail |
|---|---|
| General | • Partial dates will be displayed as captured in participant listing displays. |
| Exposure to DTG + 3TC FDC | • If the study treatment stop date is completely missing, then for the purposes of calculating exposure, it will be imputed using the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.<br>• If only the day is missing in study treatment stop date, then the last day of the month will be used, unless this is after the date of last visit or withdrawal/completion date; in this case the earliest of the three dates will be used.<br>• If only month is missing in study treatment stop date, then the last month of the year will be used, unless this is after the date of last visit or withdrawal/completion date; in this case the earliest of the three dates will be used.<br>• If both day and month are missing in study treatment stop date but year is present, then the last day of last month of the year will be used, unless this date is after the date of last visit or withdrawal/completion date; in this case the earliest of the three dates will be used.<br>• Note, Study Treatment (i.e. DTG + 3TC FDC) is recorded on the Study Treatment CRF page. |
| Adverse Events | • Partial dates for AE recorded in the CRF will be imputed using the following conventions: |

| Element | Reporting Detail |
|---|---|
| | ○ Missing start day<br>▪ If the study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.<br>▪ Else if study treatment start date is not missing:<br>• If month and year of start date = month and year of study treatment start date, then<br>○ If the stop date contains a full date and the stop date is earlier than study treatment start date, then set start date= 1st of month.<br>○ Else set start date = study treatment start date.<br>▪ Else set start date = 1st of month.<br>○ Missing start day and month<br>▪ If the study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.<br>▪ Else if study treatment start date is not missing:<br>• If year of start date = year of study treatment start date, then<br>○ If the stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.<br>○ Else set start date = study treatment start date.<br>▪ Else set start date = January 1.<br>○ Missing end day<br>▪ A '28/29/30/31' will be used for the day (dependent on the month and year).<br>○ Missing end day and month<br>▪ No Imputation<br>○ Completely missing start/end date<br>▪ No imputation |
| Concomitant Medications/Medical History | • Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:<br>○ Missing start day<br>▪ If the study treatment start day is missing (i.e. participant did not start study treatment), then set start date = 1st of month.<br>▪ Else if study treatment start date is not missing:<br>• If month and year of start date = month and year of study treatment start date, then<br>○ If the stop date contains a full date and stop date is earlier than the study treatment start date, then set start date= 1st of month.<br>○ Else set start date = study treatment start date.<br>▪ Else set start date = 1st of month.<br>○ Missing start day and month<br>▪ If the study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.<br>▪ Else if study treatment start date is not missing:<br>• If year of start date = year of study treatment start date, then<br>○ If the stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.<br>○ Else set start date = study. treatment start date.<br>○ Else set start date = January 1.<br>○ Missing end day |

| Element | Reporting Detail |
|---|---|
| | ▪ A '28/29/30/31' will be used for the day (dependent on the month and year).<br>o Missing end day and month<br>▪ A '31' will be used for the day and 'Dec' will be used for the month.<br>o Completely missing start/end date<br>▪ No imputation |
| Prior ART | • Partial dates will be imputed following the approach described for Concomitant Medications/Medical History. Then the earlier of this imputed date or the day before study treatment start date will be used.<br>• Completely missing start/end date will not be imputed. |

### 6.3.10. Trademarks

| Trademarks of the ViiV Healthcare Group of Companies |
|---|
| Dovato |
| Epivir |
| Tivicay |

| Trademarks not owned by the ViiV Healthcare Group of Companies |
|---|
| Biktarvy |
| SAS |

### 6.3.11. CDC Classification for HIV Infection (2014)

• Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing. Note that in this study, based on inclusion criteria of the study population, CDC Stage 0 is not expected.

**HIV infection, stage 0**

• Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

**HIV infection, stage 1**

• Laboratory confirmation of HIV infection with no AIDS-defining condition, and

o CD4+ T-lymphocyte count of ≥500 cells/μL, or

o CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

**HIV infection, stage 2**

• Laboratory confirmation of HIV infection with no AIDS-defining condition, and

o CD4+ T-lymphocyte count of 200 to 499 cells/μL, or

o CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

**HIV infection, stage 3 (AIDS)**

• Laboratory confirmation of HIV infection, and

o CD4+ T-lymphocyte count of <200 cells/µL, or

o CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or

o Documentation of an AIDS-defining condition (see below).

• Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/µL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

**HIV infection, stage unknown**

• Laboratory confirmation of HIV infection, and

o No information on CD4+ T-lymphocyte count or percentage, and

o No information on presence of AIDS-defining conditions.

| 2014 CDC Case Definition for HIV Infection Among Adolescents and Adults | | | |
|---|---|---|---|
| Stage | CD4 Count | CD4 %* | Clinical Evidence |
| Stage 0 | Early HIV Infection | | |
| Stage 1 | ≥500 cells/mm$^3$ | ≥26 | No AIDS-defining condition |
| Stage 2 | 200-499 cells/mm$^3$ | 14-25 | No AIDS-defining condition |
| Stage 3 | <200 cells/mm$^3$ | <14 | *or* Documentation of AIDS-defining condition |
| Stage unknown | No data | No data | *and* No information on presence of AIDS-defining conditions |
| *Use CD4 percentage only if no data available for CD4 count | | | |

**Stage-3-defining opportunistic illnesses in HIV infection**

• Candidiasis of bronchi, trachea, or lungs

• Candidiasis of oesophagus

• Cervical cancer, invasive

• Coccidioidomycosis, disseminated or extrapulmonary

• Cryptococcosis, extrapulmonary

• Cryptosporidiosis, chronic intestinal (>1 month's duration)

• Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month

• Cytomegalovirus retinitis (with loss of vision)

• Encephalopathy, HIV-related

• Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)

• Histoplasmosis, disseminated or extrapulmonary

• Isosporiasis, chronic intestinal (>1 month's duration)

• Kaposi's sarcoma

• Lymphoma, Burkitt's (or equivalent term)

• Lymphoma, immunoblastic (or equivalent term)

• Lymphoma, primary, of brain

• Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary

• Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary

• Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

• Pneumocystis jirovecii pneumonia

• Pneumonia, recurrent

• Progressive multifocal leukoencephalopathy

• Salmonella septicaemia, recurrent

• Toxoplasmosis of brain, onset at age >1 month

• Wasting syndrome attributed to HIV.

## 6.3.12. Viral Genotyping and Phenotyping

HIV-1 Resistance data for participant assessments will be provided from either Cerba or Monogram Biosciences. Cerba only provides genotypic data and Monogram can provide both genotypic (baseline and on study) and phenotypic data (only on study with plasma samples).

### Table 24 Viral Genotyping and Phenotyping

**Genotype**

**Amino Acid Changes**

- A mutation is considered present whenever the encoded amino acid residue differs from the amino acid that would have been encoded by the wild-type (e.g., HXB2, NL43) comparator gene; e.g., Q148K.
- If the encoded amino acid is seen as a mixture of wild-type and mutant amino acid, e.g., Q148Q/K, the mutated amino acid is considered present at the codon of interest.
- If the encoded amino acid is seen as a mixture of two or more amino acids, which may or may not include wild type, e.g., Q184K/H or Q184K/H/Q, etc., for the purposes of calculating the number of mutated amino acids, only one mutation is considered to be present at the codon of interest.

**Representation of Amino Acid Changes**

| Mutations | Amino acid change |
|---|---|
| T69S | Single mutation from amino acid 'T' (vendor reference) to 'S' (sample) at codon '69' |
| Q148H/K/R | Mixture of amino acid mutations 'H', 'K' and 'R' (sample) from amino acid 'Q' (vendor reference) at codon '148' |
| _69_1T | First insertion of amino acid 'T' (sample) at codon '69' |
| _69_2S | Second insertion of amino acid 'S' (sample) at codon '69' |
| _69_3S/A | Third insertion of a mixture of amino acids 'S' and 'A' (sample) at codon '69' |
| L74L/- | Mixture of amino acid 'L' (sample) and a deletion at codon '74' |
| V75- | Single deletion of amino acid (sample) at codon '75' |

**Resistance Associated Mutations**

- Known INSTI mutations associated with the development of resistance to RAL, EVG, BIC or DTG:

| | |
|---|---|
| Amino Acids in HIV Integrase for Analysis | H51Y, **T66A/I/K**, L74M, **E92Q/V**/G, Q95K, T97A, G118R, **F121Y**, E138K/A/T, G140A/C/S, **Y143C/H/R/K/S/G/A, P145S**, **Q146P**, **S147G**, **Q148H/K/R**, **V151**I/**L**/A, S153F/Y, **N155H/**S/T, E157Q, G163R/K, S230R, R263K, L68V/I*, L74I*, E138T*, V151I*, G193E* |

**NOTES:**

- Current listing includes INSTI mutations identified via the Stanford HIV Resistance database, or identified during in vitro passage of DTG*, or as seen in a previous DTG studies in INSTI-experienced participants* (i.e. ING112574) and may be modified in case of additional substantive data availability. This table of known INSTI mutations is for information and to be updated only by Virologists.
- INSTI mutations listed taken from Stanford HIV Resistance Database version 9.4.1. (https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/ cited 11Jun2023) and accessed on 14Jul2023.
- Each INSTI mutation listed had a score of ≥15. INSTI substitutions listed above in bold had a score for EVG or RAL of =60.
- Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) as defined by the International Antiviral Society-USA (IAS-USA). The most up to date IAS-USA guidelines available at the time of DBF will be used in the analysis.

| Class | Mutations |
|---|---|
| NRTIs | M41L, A62V, K65R/E/N, D67N, 69 insert, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E |
| NNRTIs | L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C/L, M230I/L, Y318F |
| PIs | D30N, V32I , M46I/L, I47A/V, G48V, I50V/L, I54M/L/V, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S, L90M |

Note: List generated from Wensing, 2022.

**Susceptibility Scores**

**Stanford Genotypic Susceptibility Score (S-GSS)**

- To establish genotypic susceptibility to ART treatment, a genotypic sensitivity score will be calculated.
- Genotypic sensitivity to each drug will be assessed using the HIVdb, the Integrated Genotypic Resistance Interpretation System [Liu, 2006].
- In the Stanford HIVdb system, each HIV-1 drug resistance mutation is assigned a drug penalty score. Also, for combination of specific mutations an extra penalty is assigned. The penalty scores for each drug resistance mutation and for combination of drug resistance mutations at different positions within each genomic region are available here.
  NNRTI: https://hivdb.stanford.edu/dr-summary/mut-scores/NNRTI/
  NRTI: https://hivdb.stanford.edu/dr-summary/mut-scores/NRTI/
  PI: https://hivdb.stanford.edu/dr-summary/mut-scores/PI/
  INSTI: https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/
- Any mutations that are not included the Stanford database will contribute 0 to the GSS calculations.
- The drug resistance estimate is obtained by adding together the penalty scores from all mutations associated with resistance to that drug and by adding also the penalty for combinations of certain mutations, if present, and then a numeric score (S-GSS) is applied for each drug as shown in the Table below.
- When there's a mixture of two or more mutations at the same position, the mutation associated with the largest penalty is scored.
- The HIVdb S-GSS will be calculated for all participants with genotypic data at all time points from when genotypic data are available for all drugs in the Stanford database. However, Tables will report S-GSS scores only for drugs that have been taken by at least one participant during the study. Listings will report S-GSS scores for all drugs in the Stanford database.
- Examples

Example 1: Assume a participant at a specific time point has the INSTI mutations G140S and Q148H. The following Table shows the calculation of drug resistance estimate score for drugs DTG and EVG.

| | Penalty Scores | |
|---|---|---|
| INSTI mutations | DTG | EVG |
| G140S | 10 | 30 |
| Q148H | 25 | 60 |
| G140S + Q148H | 10 | 0 |
| Total (drug resistance estimate) | 45 | 90 |

For DTG, mutation G140S has a penalty score of 10, mutation Q148H has a penalty score of 25. One need also to account for the penalty score for the combination of the two mutations which is 10. The sum of all penalties scores gives the drug resistance estimate score which is 45 in this case. Similar calculation for EVG applies.

Example 2: Assume a participant at a specific time point has the INSTI mutations: G140A/C/S (i.e. recorded as G140A, G140C and G140S in SDTM.PF) and Q148H/K/R. The following Table shows the calculation of drug resistance estimate score for DTG.

| | DTG | |
|---|---|---|
| INSTI mutations | Individual Mutation Penalty Score | Penalty scores used for drug resistance calculation |
| G140A | 10 | |
| G140C | 10 | 10 |
| G140S | 10 | |
| Q148H | 25 | |
| Q148K | 30 | 30 |
| Q148R | 25 | |
| G140A/C/S + Q148H/K/R | 10 | 10 |

| | |
|---|---|
| Total (drug resistance estimate) | 50 |

For mixture of mutations at the same position, the mutation associated with the largest penalty is used, hence for Q148H/K/R the penalty score of 30 for Q148K is used. For G140A/C/S all mutations have the same score 10 so, 10 is used. The penalty score for the combination of mutations at codon positions 140 and 148 is 10. The sum of the three penalties scores gives the drug resistance estimate score which is 50.

- Scores for particular patterns of INSTI, NNRTI, NRTI and PI mutations have been calculated and are readily available here
  NNRTI: https://hivdb.stanford.edu/dr-summary/pattern-scores/NNRTI/
  NRTI: https://hivdb.stanford.edu/dr-summary/pattern-scores/NRTI/
  PI: https://hivdb.stanford.edu/dr-summary/pattern-scores/PI/
  INSTI: https://hivdb.stanford.edu/dr-summary/pattern-scores/INSTI/

- The drug resistance estimate is obtained by adding together the penalty scores from all mutations associated with resistance to that drug and then a numeric score (S-GSS) is applied for each drug as shown below. Any mutations that are not included in the Stanford database will contribute 0 to the GSS calculations. When there's a mixture of two or more mutations at the same position, the mutation associated with the largest penalty is scored. The sum scores are titrated to fall within the following ranges: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance (see table below).
-

| Resistance Estimate | S-GSS Score | Sensitivity |
|---|---|---|
| **0 – 9** | **1** | **Susceptible** |
| **10 – 14** | **0.75** | **Potential low-level resistance** |
| **15 – 29** | **0.5** | **Low-level resistance** |
| **30 – 59** | **0.25** | **Intermediate resistance** |
| **≥60** | **0** | **High-level resistance** |

- The HIVdb GSS will then be calculated for each participant defined as the sum of the resistance scores for each of their background drugs.

**Monogram Genotypic Susceptibility Score (M-GSS)**

- Genotypic sensitivity to each drug will be assigned using the Monogram resistance score and will be reported in a listing for all drugs where Monogram resistance score is available in the database.
- Assays PSGT, GSIN, PSGTIN denote Genotypic Sensitivity as 'Sensitive' or 'Resistance' whereas assay GSARC as 'Sensitive', 'Resistance Possible' or 'Resistance'.
- Genotypic Sensitivity provided by Monogram based on assays PSGT, GSIN, PSGTIN is translated to a Genotypic Sensitivity Score (M-GSS) according to the table below.
- For the DTG/3TC arm a participant might have a M-GSS score of 0, 1 or 2.

| Score | Sensitivity |
|---|---|
| 1 | Sensitive |
| 0 | Resistant |

**Phenotype**

**Phenotypic Susceptibility Scores (PSS)**

- Phenotypic susceptibility to all licensed antiretroviral drugs and DTG will be determined using PhenoSense HIV assays from Monogram Inc. and will be reported as fold change (FC) in IC50 relative to wild-type control virus NL4-3, i.e., FC of sample virus = IC50 of sample virus/IC50 of control virus.
- Since the maximum assay limit for FC for each ART varies from participant to participant, FC values that are greater than the maximum assay limit (e.g., '>100') will be interpreted as having a value equal to the smallest maximum assay limit for that ART in the study population for data analysis. Censored values will be presented 'as is' in the listings.
- Phenotypic susceptibilities will be categorized according to FC (based on Monogram PhenoSense assay). Clinical cut-offs (where available) or biological cut-offs by PhenoSense will be used to define the phenotypic susceptibility of background treatment.
- Replication capacity is generated as part of standard phenotypic assays.

- To establish susceptibility to background treatment, a phenotypic sensitivity score will be calculated. Phenotypic susceptibility to each drug in a participant's background regimen will be determined by applying drug-associated cutoffs as defined by the PhenoSense algorithm to the phenotypic fold resistance to that drug at a certain timepoint (e.g., Screening or Baseline). A numeric score will be assigned to each background drug using two different methods: one with full sensitivity only (PSSf) and one with partial sensitivity included (PSSp).

**PSS with Full Sensitivity Only (PSSf)**

| Fold Change | Score | Interpretation |
|---|---|---|
| > clinical lower cutoff or biologic cutoff | 0 | resistance |
| ≤ clinical lower cutoff or biologic cutoff | 1 | sensitive |

**PSS with Partial Sensitivity Included (PSSp)**

| Fold Change | Score | Interpretation |
|---|---|---|
| > clinical higher cutoff | 0 | resistance |
| ≤ clinical higher cutoff and > clinical lower cutoff | 0.5 | partially sensitive |
| ≤ clinical lower cutoff | 1 | sensitive |

- Both PSSf and PSSp will be calculated separately for each participant defined as the sum of the resistance scores for each background drug.

| Drug | Abbreviation | Class | PhenoSense cutoff |
|---|---|---|---|
| Abacavir | ABC | NRTI | (4.5 – 6.5)[a] |
| Lamivudine | 3TC | NRTI | 3.5[a] |
| Didanosine | ddI | NRTI | (1.3 – 2.2)[a] |
| Stavudine | d4T | NRTI | 1.7[a] |
| Zidovudine | AZT (ZDV) | NRTI | 1.9 |
| Emtricitabine | FTC | NRTI | 3.5 |
| Tenofovir | TDF | NRTI | (1.4 – 4)[a] |
| Delavirdine | DLV | NNRTI | 6.2 |
| Efavirenz | EFV | NNRTI | 3 |
| Nevirapine | NVP | NNRTI | 4.5 |
| Etravirine | ETR | NNRTI | (2.9-10)[a] |
| Rilpivirine | RPV | NNRTI | 2.0 |
| Fosamprenavir/r | FPV/r | PI | (4-11)[a] |
| Atazanavir/r | ATV/r | PI | 5.2[a] |
| Indinavir/r | IDV/r | PI | 10[a] |
| Lopinavir/r | LPV/r | PI | (9 – 55)[a] |
| Nelfinavir | NFV | PI | 3.6 |
| Saquinavir/r | SQV/r | PI | (2.3 – 12)[a] |
| Tipranavir/r | TPV/r | PI | (2 – 8)[a] |
| Darunavir/r | DRV/r | PI | (10 – 90)[a] |
| Ritonavir | RTV | PI | 2.5 |
| Enfuvirtide | T20 | FI | 6.48 |
| Raltegravir | RAL | INSTI | 1.5 |
| Elvitegravir | EVG | INSTI | 2.5 |
| Dolutegravir | DTG | INSTI | (4-13)[a] |
| Bictegravir | BIC | INSTI | (2.5-10) |

a. clinical cutoff (lower cutoff – higher cutoff)

**Phenotypic Susceptibility Score (PSS)**

**Net Assessment and Overall susceptibility of ARTs**

- Net assessment is an assessment of antiviral activity of ARTs using both genotypic and phenotypic test results interpreted through a proprietary algorithm (from Monogram Biosciences) and provides the overall susceptibility of the drug (Note: partially sensitive and resistant calls are considered resistant in this analysis).
- For determining overall susceptibility of ARTs (OSS), a binary scoring system (0= resistant, 1=sensitive) for each antiretroviral agent was used and will be provided in the Monogram dataset. OSS will be calculated as the sum of the net assessment scores of ARTs comprising the participant's ART and categorized as 0, 1, 2, or 3. OSS values will be calculated only for the time of CVW when net assessment is available.

**Decision tree approach for Monogram resistance data analyses**

- We might have resistance data that come from mixed datasets: PSGT, PSIN, GSIN (primary assays) vs PSGT+IN (secondary assay)
- If one of the primary assay does not work for a specific timepoint, we might report the secondary assay if data is available. If all primary assays for a specific timepoint work then we report primary. For example, for baseline if the same assay section (PSGT, PSIN, GSIN) worked then we report primary. If at least one of PSGT or PSIN or GSIN didn't work then we report secondary PSGT+IN.
- Secondary assay testing results might not always be available.

**Background:**

- PSGT - provides both geno and pheno data for PRO/RT (NRTI and NNRTI) only, with pheno including PRO/RT Replication Capacity (RC)
- PSIN - Provides pheno data on Integrase only, with pheno including IN RC
- GSIN - Provides geno data on Integrase only, This assay provides NO RC data.
- PSGT+IN - Secondary assay used if PSGT or GSIN assay fails; it provides both geno and pheno data on PRO, RT and Integrase

- If one of the primary assays does not work for a specific timepoint, we might report the data from the secondary assay, if available. If all primary assays for a specific timepoint work, then we use the data from the primary assays, as secondary assay analysis is not performed. If at least one of PSGT or PSIN or GSIN haven't worked for a specific time point (e.g. Baseline, CVF or time of switch from DTG + 3TC FDC), then we use data from the secondary PSGT+IN and the data from any primary assay that worked from this time point are ignored.
- Secondary assay testing results might not always be available.
- The decision tree algorithm will be used for data summaries in Tables. Listings will report all data from all assays that worked at a specific time point.
- For examples please refer to decision tree below.

**Table Symbol Key:**

Y = assay test successful
N = assay test failure
2nd = back up test performed
**bold** = assay to use for analysis

**How to make decisions:**

Scenario 1: if primary PSGT, PSIN and GSIN assays all work for both Baseline and CVF or at time to switch due to Baseline resistance mutations samples, then PSGT+IN assay will not be performed and no PSGT+IN data should be generated.

| Assays | Baseline | CVF or Switch |
|---|---|---|
| PSGT | **Y** | **Y** |
| PSIN | **Y** | **Y** |
| GSIN | **Y** | **Y** |

Scenario 2: If PSGT, PSIN and GSIN all work for Baseline sample; PSGT works for CVF or at time of Switch sample but PSIN and GSIN fail, while PSGT+IN works, then use PSGT+IN (PR, RT and INSTI) for CVF/Switch and a PSGT, PSIN, GSIN for Baseline; do not use PSGT data at CVF/Switch.

| Assays | Baseline | CVF or Switch |
|---|---|---|
| PSGT | **Y** | Y |
| PSIN | **Y** | N |
| GSIN | **Y** | N |
| 2nd PSGT+IN | - | **Y** |

Scenario 3: If PSGT works for Baseline, but PSIN and GSIN fail, then secondary PSGT+IN assay will be performed on Baseline sample. Similarly, if PSGT works for CVF or switch sample but PSIN and GSIN fail to work, in this scenario, use data generated from PSGT+IN assay on both Baseline and CVF/switch sample for analyses, regardless of obtained PSGT assay data. Same is the case if PSGT fails in both time points and PSIN and GSIN do not fail; the data from PSGT+IN from both time points will be used.

| Assays | Baseline | CVF or Switch |
|---|---|---|
| PSGT | Y | Y |
| PSIN | N | N |
| GSIN | N | N |
| 2nd PSGT+IN | **Y** | **Y** |

Scenario 4: If PSGT works but GSIN and PSIN both fail on Baseline sample, then 2nd PSGT+IN assay might be performed. If PSGT, PSIN and GSIN all work for CVF or Switch sample, then use Baseline PSGT+IN data from Baseline, regardless of PSGT Baseline data.

| Assays | Baseline | CVF or Switch |
|---|---|---|
| PSGT | Y | **Y** |
| PSIN | N | **Y** |
| GSIN | N | **Y** |
| 2nd PSGT+IN | **Y** | - |

## 6.4. Appendix 4 Schedule of Activities

### Table 25 Schedule of Activities

| Procedure | Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent) | | | | Treatment Phase[a, v] (DTG/3TC) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 to 2 data collection time points at -48 Wks to Screening | Screening | Day 1 | Wk 4 ±6 days | Wk 12 ±6 days | Wk24± 6 days | Wk48 ±6 days | Wk72 ±6 days | Wk96 ±6 days | Withdrawal[w] | Follow-Up Visit[x] |
| Written Informed Consent[c] | | X | | | | | | | | | |
| Eligibility Verification (Inclusion/ Exclusion Criteria) | | X | X | | | | | | | | |
| Demography | | X | | | | | | | | | |
| Medical History[d] | | X | | | | | | | | | |
| Current medical conditions | | X | | | | | | | | | |
| Medication History including Complete Prior ART history | | X | | | | | | | | | |
| Cardiovascular risk assessment[d] | | X | X | | | X | X | | X | | |
| Syphilis serology + reflex Rapid Plasma Reagin (RPR) | | X | X | | | | | | | | |

| Procedure | Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent) | | | Treatment Phase[a, v] (DTG/3TC) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 to 2 data collection time points at -48 Wks to Screening | Screening | Day 1 | Wk 4 ±6 days | Wk 12 ±6 days | Wk24± 6 days | Wk48 ±6 days | Wk72 ±6 days | Wk96 ±6 days | Withdrawal[w] | Follow-Up Visit[x] |
| Symptom Directed Physical Exam and Medical Assessment[e] | | X | X | X | X | X | X | X | X | X | X |
| Weight, Height and BMI[f] | X | X | X | X | X | X | X | X | X | X | |
| Waist Circumference[f] | | | X | | | X | X | | X | X | |
| Hip Circumference[f] | | | X | | | X | X | | X | X | |
| Vital Signs (BP, HR)[g] | X | X | X | X | X | X | X | X | X | X | |
| 12-lead ECG[h] | | | X | | | | | | | | |
| Retrospective Hematology (CD4, including CD4 Nadir, CD8, Platelets) Clinical Chemistry (Creatinine, eGFR and liver chemistry [ALT, AST, GGT, total and direct bilirubin]) as available | X | | | | | | | | | | |

| Procedure | Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent) | | | Treatment Phase[a, v] (DTG/3TC) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 to 2 data collection time points at -48 Wks to Screening | Screening | Day 1 | Wk 4 ±6 days | Wk 12 ±6 days | Wk24± 6 days | Wk48 ±6 days | Wk72 ±6 days | Wk96 ±6 days | Withdrawal[w] | Follow-Up Visit[x] |
| CDC HIV-1 stage[i] | | X | X | | | | | | | | |
| HIV Associated Conditions | | | X | X | X | X | X | X | X | X | X |
| AEs, SAEs, Concomitant Medications[j] | | X | X | X | X | X | X | X | X | X | X |
| Electronic Columbia Suicidality Severity Rating Scale (eC-SSRS)[k] | | X | X | | X | X | X | | X | X | |
| Clinical chemistry | | X | X | X | X | X | X | X | X | X | X |
| Hematology | | X | X | X | X | X | X | X | X | X | X |
| Pregnancy Testing[l] | | S | S/U | U | U | U | U | U | U | S | U |
| HIV-1 RNA quantitation and sample(s) for storage[m] | | X | X | X | X | X | X | X | X | X | X |
| CD4+ cell count | | | X | X | X | X | X | X | X | X | X |
| CD8+ cell count | | | X | | | X | X | | X | X | |
| Urinalysis[n] | | | X | X | | X | X | | X | X | |

| Procedure | Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent) | | | Treatment Phase[a, v] (DTG/3TC) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 to 2 data collection time points at -48 Wks to Screening | Screening | Day 1 | Wk 4 ±6 days | Wk 12 ±6 days | Wk24± 6 days | Wk48 ±6 days | Wk72 ±6 days | Wk96 ±6 days | Withdrawal[w] | Follow-Up Visit[x] |
| Fasting Labs: Glucose, Insulin, HbA1c, Cholesterol (Total, HDL and LDL) and Triglycerides[o] | X | | X | | | X | X | | X | X | |
| Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG, Hepatitis C (anti-HCV Ab) | | X | | | | | | | | | |
| PT/PTT/INR | | X | X | | | | | | | | |
| Whole Blood (Virology)[p] | | | X | | | X | X | | X | X | |
| PBMCs[p] | | | X | | | | X | | X | X | |
| Renal, and bone biomarker analytes (blood and urine)[q] | | | X | | | X | X | | X | X | |
| Liver Fibroscan | | | X | | | | X | | X | | |
| DXA Scan for Body Composition[r] | | | X | | | | X | | X | | |
| HIV TSQs[s] | | | X | | | X | | | X | X | |
| HIV TSQc[s] | | | | | | | X | | | | |

| Procedure | Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent) | | Treatment Phase[a, v] (DTG/3TC) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 to 2 data collection time points at -48 Wks to Screening | Screening | Day 1 | Wk 4 ±6 days | Wk 12 ±6 days | Wk24± 6 days | Wk48 ±6 days | Wk72 ±6 days | Wk96 ±6 days | Withdrawal[w] | Follow-Up Visit[x] |
| Symptom Distress Module[s] | | | X | | | X | X | | X | X | |
| WHOQOL-HIV BREF[s] | | | X | | | X | X | | X | X | |
| Menopause Rating Scale (MRS) questionnaires | | | X | | | | | | | | |
| Bespoke Participant Questionnaires (HO & ImpSc)[s] | | | X | | | X | X | | X | | |
| Bespoke Provider Questionnaires (HO & ImpSc)[t] | | | X | | | X | X | | X | | |
| Participant Interviews (HO & ImpSc)[u] | | | X | | | X | X | | X | | |
| Provider Interviews (HO & ImpSc)[u] | | | X | | | X | X | | X | | |
| Control of Eating Questionnaire (CoEQ). See 4.4.1 | | | X | X | X | | X | | X | | |

| Procedure | Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent) | | | Treatment Phase[a, v] (DTG/3TC) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 to 2 data collection time points at -48 Wks to Screening | Screening | Day 1 | Wk 4 ±6 days | Wk 12 ±6 days | Wk24± 6 days | Wk48 ±6 days | Wk72 ±6 days | Wk96 ±6 days | Withdrawal[w] | Follow-Up Visit[x] |
| Actigraphy and Participant Health Self Reporting App[v] | | X | X | X | X | X | X | X | | | |
| Dispense Study Treatment | | | X | | X | X | X | X | | | |
| Study Treatment accountability | | | | X | X | X | X | X | X | X | X |

Note: BP – Blood pressure, HR – Heart Rate, BMI – Body Mass Index, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, PT - Prothrombin Time, PTT - Partial Thromboplastin Time, INR - International normalized ratio, PBMC – peripheral blood mononuclear cell, RNA – Ribonucleic acid, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, HO – Health Outcome, ImpSc: Implementation Science.

a. The acceptable window around any visit, post Day 1 is ±6 days. Participant must come in no later than +6 days of the visit windows or participant will run out of drug supply.
b. Complete all Screening assessments within 28 days. Participants may begin the Treatment Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number. Collect gender identity and sex at birth/sex at time of study entry.
c. Refer to the study protocol Section 10.1.3 for informed consent process. Enrolled participants should be re-consented using the latest approved version of the ICF, as applicable.
d. Collect full routine medical history plus (report at Baseline visit): Cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal, bone, and neurologic disorders. At Screening, Day 1, Week 24, Week 48 and Week 96 visits assessments inclusive of smoking status, alcohol use and illicit drug use since the start of the study will be performed.
e. Physical exams should be conducted as part of normal routine clinical care. Medical assessments include any decisions the study staff must make for participants management and/or care of participant.
f. Height collected at Baseline Day 1 only. Recommended procedures to measure weight, waist and hip circumference can be found in the study protocol Section 10.12.
g. Measure vital signs after about 5 minutes of rest in a semi-supine position.

h. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
i. When assessing CDC stage at Screening/Baseline, consider only the latest available CD4 T-cell count, except when the participant had an active Stage 3 event 6 months prior to Screening.
j. Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GSK product will be collected between obtaining informed consent and administration of study treatment at Day 1
k. eC-SSRS will be completed at the beginning of the visit after administration of any other PROs, and prior to administration of study treatment. On Day 1, eC-SSRS is to be administered prior to the first dose.
l. Women of childbearing potential only. S=serum; U=urine. Pregnancy events will be captured starting at Day 1 following first dose of study treatment. Serum pregnancy test can substitute for urine pregnancy test if locally required but must be appropriately timed to confirm pregnancy status prior to enrolment and first dose of study treatment (as applicable). Where both serum and urine tests (S + U) are indicated for a given visit, proceed based on the result of the urine test, and review serum test result once available. If urine test is positive at Day 1, perform a serum test and do not administer study treatment. The frequency of pregnancy tests should be performed according to local requirements. Do not perform the assessment for participants already confirmed to be pregnant based on results of a prior test.
m. Plasma samples will be collected at each visit starting at Screening, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples may also be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or particularly for virologic resistance analyses when participants meet Suspected and Confirmed Virologic Withdrawal criteria. Plasma and serum samples may also be used for further post-hoc assessments of relevant cardio-metabolic, inflammation biomarkers or virology tests that may assist with the understanding of any study finding. Retain frozen; refer to lab manual for specific handling instructions.
n. A morning specimen is preferred. To assess biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; urine phosphate; beta-2-microglobulin; and retinol binding protein.
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable. Blood sample for insulin and HbA1c.
p. Whole blood/PBMC collection samples may be used for virologic analyses.
q. Blood sample for renal and bone biomarker assessments: **Renal:** CystatinC; 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.
r. A +6 weeks window is allowed. Refer to the study protocol Section 8.3.5 for full details. Pregnancy testing should be performed for women of childbearing potential, and results available, before the DXA scan; the radiation procedures will not go ahead without a confirmed negative pregnancy test. Repeat DXA scans will be avoided wherever possible, no more than 1 repeat is allowed.
s. All PROs are recommended to be administered before other assessments take place at each designated visit. PRO will be completed electronically by participants. For MRS: MRS questionnaire available at https://www.hormonebalance.org/files/MRS%20QOL%20questionnaire%20.pdf
t. Provider interviews will occur after the first participant at the site had completed the corresponding visit e.g. Week 24 interview conducted, after first participant at the site performed their Week 24 visit.
u. Participant and Provider qualitative interviews will only be conducted in the US, UK and Canada.
v. Refer to the study protocol Section 8.13 and SRM.
w. Refer to Section 7 of the protocol for additional information on performing withdrawal assessments.
x. A Safety Follow-Up visit will be conducted 2-4 weeks after the last dose of study intervention for participants who meet specific criteria as described in Section 4.4.1. Only the assessments necessary to evaluate the AE/SAE/laboratory abnormality should be collected.
y. The baseline fibroscan should be completed on Day 1; however, a +6 week window is permittable if necessary due to operational delays.

## 6.5. Appendix 5 Snapshot Algorithm Details

- Consider an analysis visit window, Week X (e.g., Week 24, Week 48). The Window for Week 24/48 visit is defined in Table 22.
- Consider an HIV1-RNA threshold (e.g., 40, 50, 200 copies/mL …) in analysis,

- The analysis window 'Week 48' and HIV1-RNA threshold of '50 c/mL' are used for the purpose of illustration. A participant's Snapshot response and reason at Week 48 are categorized as below.
  - HIV1-RNA < **50** copies/mL
  - HIV1-RNA ≥ **50** copies/mL

    Data in window not below 50

    Discontinued for lack of efficacy

    Discontinued for other reason while not below 50

    Change in background therapy*
  - No Virologic Data at Week 48 Window

    Discontinued study due to AE or death

    Discontinued study for other reasons

    On study but missing data in window

* Note: since changes in ART or dose modification are not permitted in this protocol, all such participants who change ART during Treatment Phase will be considered 'HIV1-RNA ≥ 50 c/mL' if the change in ART is made prior to an analysis timepoint.

The steps in determining response and reasons are indicated in the Table below, in the order stated.

**Detailed steps**

- Please note that the following scenarios will NOT be penalized Per Snapshot algorithm (i.e., please excluding these scenarios from **Condition** 1-4).
  - Dose reduction, dropping a component, or change in formulation (e.g. 'Tivicay + Kivexa' to 'Triumeq' with the identical ingredients)
  - Permitted Change (if a decision date is not collected in eCRF) / decision to permitted change is made prior to/on the first on-treatment viral load result
  - Permitted change is made after the first on-treatment viral load result AND last on-treatment viral load prior to/on the date of change is <50 c/mL

| **Condition**<br>('Week 48' indicates Week 48 window) | **Response** | **Reasons** |
|---|---|---|
| 1. If ***non-permitted*** change in background therapy ***prior to*** Week 48 | HIV1-RNA ≥ 50 | Change in background therapy |
| 2. If ***permitted*** change in background therapy ***prior to*** Week 48 AND the latest on-treatment VL prior to/on the date of change is ≥ 50 c/m [a] | HIV1-RNA ≥ 50 | Change in background therapy |
| 3. If ***non-permitted*** change in background therapy ***during*** Week 48 | | |

| | | |
|---|---|---|
| • 3.1 Last on-treatment VL during Week 48 prior to/on the date of change ≥ 50 c/mL | HIV1-RNA ≥ 50 | Data in window not below 50 |
| • 3.2 Last on-treatment VL during Week 48 prior to/on the date of change <50 c/mL | HIV1-RNA < 50 | |
| • 3.3 No VL during Week 48 prior to/on the date of change | HIV1-RNA ≥ 50 | Change in background therapy |
| 4. If ***permitted*** change in background therapy ***during*** Week 48 AND the last on-treatment VL prior to/on the date of change is ≥ 50 c/mL [a] | | |
| 4.1 this last on-treatment VL occurs prior to Week 48 | HIV1-RNA ≥ 50 | Change in background therapy |
| 4. 2 this last on-treatment VL occurs during Week 48 but prior to/on the date of change | HIV1-RNA ≥ 50 | Data in window not below 50 |
| 5. If none of the above conditions met | | |
| 5.1 VL available during Week 48 | | |
| 5.1.1 Last on-treatment VL during Week 48 ≥ 50 c/mL | HIV1-RNA ≥ 50 | Data in window not below 50 |
| 5.1.2 Last on-treatment VL during Week 48 <50 c/mL | HIV1-RNA < 50 | |
| 5.2 No VL during Week 48 | | |
| 5.2.1 If participants still on study (i.e. The on-treatment period has not been ended up to the upper bound of Week 48 window. For example, for oral treatment, the on-treatment period ends at permanently IP stop date+1) | No virologic data at Week 48 Window | On study but missing data in window |
| 5.2.2 If participants withdraw before/during Week 48 due to :- | | |
| 5.2.2.1 Safety reasons (e.g. AE/death, liver chemistry stopping criteria, renal toxicity withdrawal criteria, QTc withdrawal criteria et al, as recorded in eCRF Study Conclusion form) | No virologic data at Week 48 Window | Disc. due to AE/death |
| 5.2.2.2 Non-safety related reasons (e.g. Lack of efficacy, protocol deviation, withdrew consent, loss to follow-up, study closed/terminated, investigator discretion et al, as recorded in eCRF Study Conclusion Form) | | |
| 5.2.2.2.1 Last on-treatment VL <50 c/mL OR no on-treatment VL available during study | No virologic Data at Week 48 Window | Disc. for other reasons |
| 5.2.2.2.2 Last on-treatment VL ≥ 50 c/mL AND withdrawal due to Lack of efficacy | HIV1-RNA ≥ 50 | Disc. for lack of efficacy |
| 5.2.2.2.3 Last on-treatment VL ≥ 50 c/mL AND withdrawal due to all other non-safety related reasons | HIV1-RNA ≥ 50 | Disc. for other reason while not below 50 |

[a]: Excluding permitted change in background therapy where change or decision to change is made prior to/on the first on-treatment viral result

## Examples from FDA guidance

Data in Window

Virologic outcome should be determined by the last available measurement while the participant is on treatment and continued on trial within the time window:

- HIV-RNA = 580 copies/mL at Day 336, HIV-RNA below 50 copies/mL on Day 350. This should be categorized as HIV-RNA below 50 copies/mL.

No Data in Window

Discontinued study due to Adverse Event or Death:

- Any participant who discontinues because of an AE or death before the window should be classified as *Discontinued due to AE or Death* (as appropriate), regardless of the HIV-RNA result, even if the HIV-RNA is below 50 copies/mL at the time of discontinuation.
- However, if a participant has an HIV-RNA value in the time window and also discontinues in the time window, the viral load data should be used to classify the participant's response. This is the Virology First hierarchy:
    a. HIV-RNA below 50 copies/mL at Day 336 and discontinues because of AE or even dies on Day 360 — this person is categorized as having HIV-RNA below 50 copies/mL.
    b. HIV-RNA is 552 copies/mL on Day 336 and the participant discontinues on Day 360, the participant is categorized as having HIV-RNA greater than or equal to 50 copies/mL.

Discontinued for Other Reasons:

- Only participants who have achieved virologic suppression can be counted as *Discontinued for Other Reasons.*
- If a participant discontinues the study before the window because of *lack of efficacy* then the participant should be included in the HIV-RNA greater than or equal to 50 row and not in the Discontinued for Other Reasons row.
- If a participant discontinues because of *consent withdrawal* and his or her HIV-1 RNA result at the time of discontinuation was equal to or above 50 copies/mL, then he or she should be categorized as HIV-RNA greater than or equal to 50 and NOT as Discontinued for Other Reasons.
- If a participant discontinued because of *lost to follow-up* and the last HIV-RNA result was 49 copies/mL, then the participant can be categorized as Discontinued for Other Reasons.
- If participants changed background treatment — *not permitted by protocol*— they should be considered an efficacy failure and captured in the HIV-RNA greater than or equal to 50 copies/mL row.

On study but missing data in window:

- If there are no data during Days 294 to 377, but there is an HIV-RNA below 50 copies/mL on Day 380, this participant should be considered *On Study but Missing Data in Window.*
- If there are no data during Days 294 to 377, but there is an HIV-RNA equal to or above 50 copies/mL on Day 280, this participant also should be classified as *On Study but Missing Data in Window.*

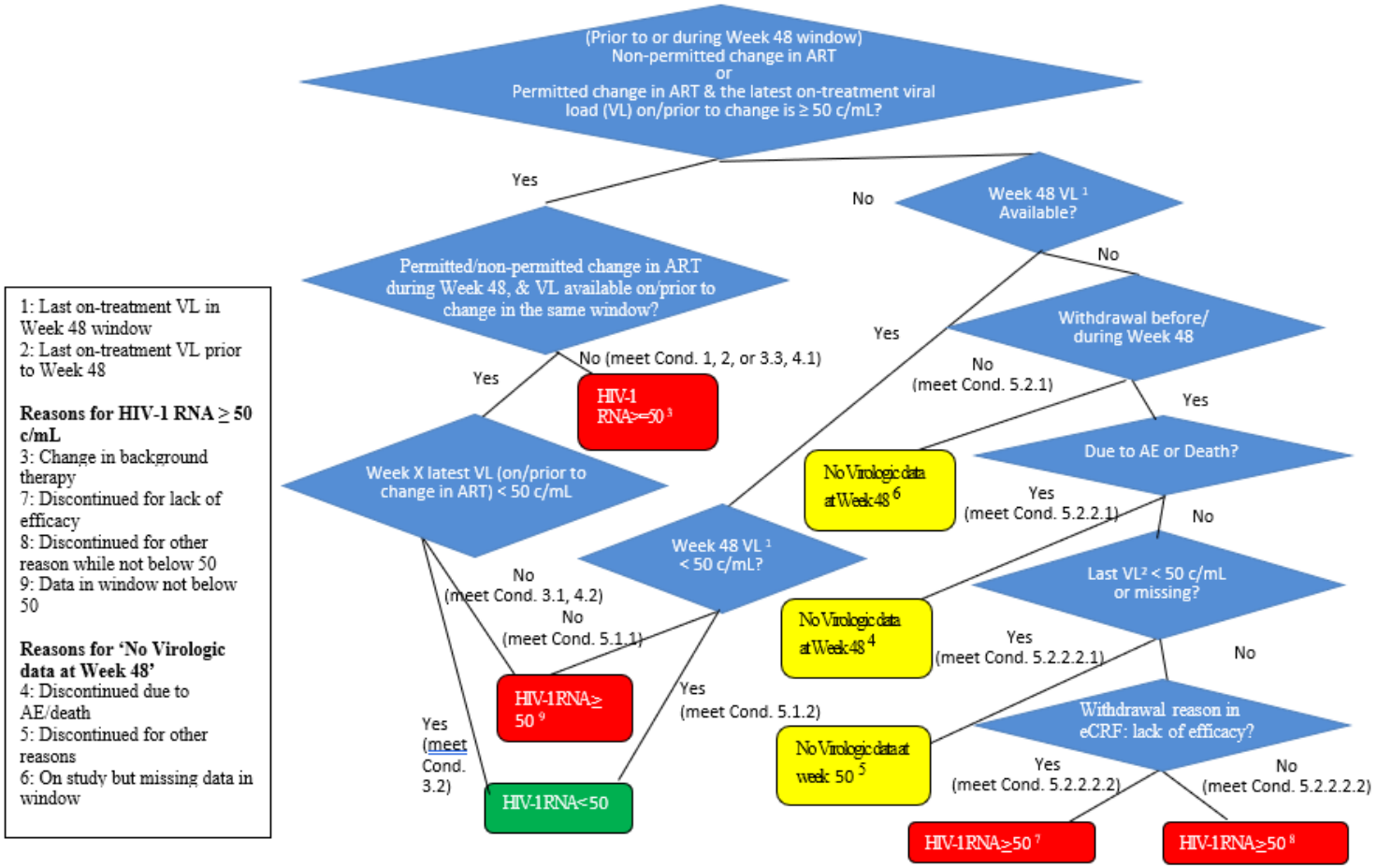
Optimized Background Therapy Substitutions After Randomization

- OBT substitutions (in-class or cross-class) permitted per protocol for documented toxicity reasons can be permitted on or before the first trial visit without penalty.

If OBT substitutions for toxicity reasons occur after the first trial visit, then participants should be categorized as having HIV-RNA greater than or equal to 50 copies/mL if they have HIV-RNA above 50 copies/mL at the time of switch.

Snapshot outcomes are shown below and are to be used in conjunction with the steps in the Snapshot algorithm.

**Figure 1 Flowchart of Snapshot Outcome**



A dataset will be created based on the Snapshot algorithm, where the dataset contains the following information, as a minimum:

- Study identification
- Participant identification
- Study day and date of last treatment
- Virologic outcome based on the snapshot approach (i.e., HIV-1 RNA < 50 c/mL, HIV-1 RNA ≥ 50 c/mL, discontinued due to AE or death, discontinued for other reasons, on study but missing data during window)
- The HIV-1 RNA measurement and the corresponding study day and date used to determine the above virologic outcome if the measurement was not missing
- Study day and date when the participant switched to open-label treatment due to lack or loss of virologic suppression, if applicable
- Discontinuation study day and date, reason for discontinuation, and last treatment measurement before discontinuation for participants who discontinued study drug.

## 6.6. Appendix 6 Time to Event Details

### 6.6.1. TRDF Detailed Steps

<table>
<tr><th colspan="3">TRDF Detailed steps</th></tr>
<tr><td colspan="3">The steps below are for the derivation of TRDF at specific timepoints when the upper bound of the analysis window is used as a cut-off i.e. for the table only.</td></tr>
<tr><td colspan="3">Final step of the derivation is made in following order:<br><br>[1] When one EVENT (1.2, 2.2, 3.2, 4.2) criterion is satisfied, select. In situations where more than one EVENT criteria satisfied, select the earliest event. If the earliest event date satisfies more than one criteria (e.g. participant had CVW and discontinuation), select CVW.<br><br>[2] When one CENSOR (1.1, 2.1, 3.1, 4.1, 5.x) criterion is satisfied, select. Else in situations where more than one CENSOR criteria satisfied, select the latest censor day. If the latest event date satisfies more than one criteria, apply the ordering below.</td></tr>
<tr><th>Condition</th><th>Censor Status</th><th>Event Description/AVAL</th></tr>
<tr><td>1. Participants met CVW event criteria<br><br>(Based on derived CVW confirmed prior to cut-off used for the analysis)</td><td></td><td></td></tr>
</table>

| | | |
|---|---|---|
| Then set **tempAVAL**= Study Day of first elevation | | |
| 1.1 CVW event date is after the upper bound of the analysis visit window<br><br>i.e tempAVAL > upper bound of the analysis visit window for Week X | CNSR=1 | EVNTDESC=Censored due to data cutoff.<br><br>AVAL=Upper bound of analysis visit window. |
| 1.2 CVW event date is on or before the upper bound of the analysis visit window<br><br>i.e tempAVAL ≤ upper bound of the analysis visit window for Week X | CNSR=0 | EVNTDESC=CVW.<br><br>AVAL= tempAVAL. |
| 2. Participants with study withdrawal due to treatment related adverse events<br><br>(defined as participants that have reason for withdrawal =AE on disposition page and that the participant has at least one AE considered both: i) drug related (AEREL=Y) and ii) result in withdrawal from study (AEWD=Y))<br><br>Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study Day of permanent treatment discontinuation [from Exposure and Concomitant ART domains]).<br><br>Assumption: Study Day of permanent treatment discontinuation is included in the definition to account for cases where discontinuation information is recorded later. This is a conservative approach consistent with treatment discontinuation preceding withdrawal. | | |
| 2.1 Study withdrawal is after the upper bound of the analysis visit window | CNSR=1 | EVNTDESC=Censored due to data cutoff. |

| | | |
|---|---|---|
| i.e tempAVAL > upper bound of the analysis visit window | | AVAL=Upper bound of analysis visit window. |
| 2.2 Study withdrawal is on or before the upper bound of the analysis visit window<br><br>i.e tempAVAL ≤ upper bound of the analysis visit window | CNSR=0 | EVNTDESC=Study Withdrawal Due to Treatment Related AE.<br><br>AVAL= tempAVAL |
| 3: Participants met protocol defined stopping criteria [1]<br><br>(Based on disposition page)<br><br>Then set **tempAVAL**=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or Concomitant ART Therapy (CONART) eCRF pages]).<br><br>Note [1]: Excludes participants who met protocol defined stopping criteria due to Virologic Withdrawal criteria | | |
| 3.1 Protocol defined stopping criteria were met after the upper bound of the analysis visit window<br><br>i.e tempAVAL > upper bound of the analysis visit window | CNSR=1 | EVNTDESC=Censored due to data cutoff.<br><br>AVAL=Upper bound of analysis visit window. |
| 3.2 Protocol defined stopping criteria were met on or before the upper bound of the analysis visit window<br><br>i.e tempAVAL ≤ upper bound of the analysis visit window | CNSR=0 | EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria.<br><br>AVAL=tempAVAL |

| | | |
|---|---|---|
| 4: Participants with study withdrawal due to lack of efficacy [2]<br><br>(Based on disposition page)<br><br>Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages])<br><br>Note [2]: For sensitivity analysis, participants withdrawn under PA02 who are not CVWs under PA03 do not meet this condition. Instead they will be categorized under condition 5. | | |
| 4.1 Study withdrawal is after the upper bound of the analysis visit window<br><br>i.e tempAVAL > upper bound of the analysis visit window<br><br>See Note [2] above. | CNSR=1 | EVNTDESC=Censored due to data cutoff.<br><br>AVAL=Upper bound of analysis visit window. |
| 4.2 Study withdrawal is on or before the upper bound of the analysis visit window<br><br>i.e tempAVAL ≤ upper bound of the analysis visit window<br><br>See Note [2] above. | CNSR=0 | EVNTDESC=Study Withdrawal Due to Lack of Efficacy<br><br>AVAL= tempAVAL |
| **If none of the above conditions met** | | |
| 5: Participants with study withdrawal for other reasons<br><br>(Based on disposition page)<br><br>Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study | | |

| | | |
|---|---|---|
| day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages]) | | |
| 5.1 Study withdrawal is after the upper bound of the analysis visit window<br><br>i.e tempAVAL > upper bound of the analysis visit window | CNSR=1 | EVNTDESC=Censored due to data cutoff.<br><br>AVAL=Upper bound of analysis visit window. |
| 5.2 Study withdrawal is on or before the upper bound of the analysis visit window<br><br>i.e tempAVAL ≤ upper bound of the analysis visit window | CNSR=1 | EVNTDESC=Censored due to Study Discontinuation for Other Reasons.<br><br>AVAL=tempAVAL |
| 6: Participant completed the study.<br><br>(Based on disposition page) | CNSR=1 | EVNTDESC= Censored as completed<br><br>AVAL= Date of end of Treatment Phase |
| 7: Participant is ongoing in the study and have not yet completed<br><br>Assumption: this will only be in cases where the reporting effort/analysis is performed midway through the study | CNSR=1 | EVNTDESC= Censored due to data cutoff.<br><br>AVAL=Upper bound of analysis visit window. |

### 6.6.2. TRDF Detailed Steps for the Kaplan-Meier plot

| TRDF Detailed steps |
|---|
| **The steps below are for the derivation of TRDF overall i.e. for the Kaplan-Meier plot only.** |
| Final step of the derivation is made in following order:<br><br>[1] When one EVENT (conditions 1-4) criterion is satisfied, select. In situations where more than one EVENT criteria satisfied, select the earliest event. If the earliest event date satisfies more than one criteria (e.g. participant had CVW and discontinuation), select CVW.<br><br>[2] When one CENSOR (conditions 5.x) criterion is satisfied, select. Else in situations where more than one CENSOR criteria satisfied, select the latest censor day. If the latest event date satisfies more than one criteria, apply the ordering below. |

| Condition | Censor Status | Event Description/AVAL |
|---|---|---|
| 1. Participants met CVW event criteria during study<br><br>(Based on derived CVW confirmed prior to cut-off used for the analysis) | CNSR=0 | EVNTDESC=CVW.<br><br>AVAL= Day of CVW. |
| 2. Participants with study withdrawal due to treatment related adverse events during the randomized period<br><br>(defined as participants that have reason for withdrawal =AE on disposition page and that the participant has at least one AE considered both: i) drug related (AEREL=Y) and ii) result in withdrawal from study (AEWD=Y)) | CNSR=0 | EVNTDESC=Study Withdrawal Due to Treatment Related AE.<br><br>AVAL=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages]). |
| 3: Participants met protocol defined stopping criteria during the study [1]<br><br>(Based on disposition page)<br><br>Note [1]: Excludes participants who met protocol defined stopping criteria due to Virologic Withdrawal criteria | CNSR=0 | EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria.<br><br>AVAL=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages]). |
| 4: Participants with study withdrawal due to lack of efficacy during the study [2]<br><br>(Based on disposition page)<br><br>Note [2]: For sensitivity analysis, participants withdrawn under PA02 who are not CVWs under PA03 do not meet this condition. Instead they will be categorized under condition 5. | CNSR=0 | EVNTDESC=Study Withdrawal Due to Lack of Efficacy<br><br>AVAL= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages]) |

| **If none of the above conditions met** | | |
|---|---|---|
| 5: Participants with study withdrawal for other reasons on or before the end of study.<br><br>(Based on disposition page) | CNSR=1 | EVNTDESC=Censored due to Study Discontinuation for Other Reasons.<br><br>AVAL=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages]) |
| 6: Participant completed the study.<br><br>(Based on disposition page) | CNSR=1 | EVNTDESC= Censored as completed the study.<br><br>AVAL= Date of completion of study |
| 7: Participant is ongoing in the study and have not yet completed the randomized period | CNSR=1 | EVNTDESC= Ongoing in the Study.<br><br>AVAL=Last visit date |

**Notes:**
Randomized Period = Randomized Phase
Efficacy visit windows should be used throughout for the upper bound of the analysis visit window
Participants are considered to have completed the study if they completed the 96 weeks (EOS) visit and the follow-up
By definition, a participant must be on-treatment for a CVW to be recorded therefore inclusion of study date of treatment discontinuation in the derivation is not required
EVNTDESC, AVAL & CNSR variables created for the following timepoints:
Week 24 or 48 or 96 – for the table analysis
Overall – for the Kaplan-Meier plot

### 6.6.3. ERDF Detailed Steps

Similar algorithm will be applied for ERDF analyses and Kaplan-Meier figure, where condition 2 and 3 in Section 6.6.1 and Section 6.6.2 will not be considered.

## 6.7. Appendix 7 Sub-study

- Eligible participants are those who withdraw from study 219516 due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria, lack of efficacy). Participants impacted by virologic-management related concerns (e.g., viral load elevations) prior to withdrawal from 219516 for other reasons (e.g., AE/SAE, withdrawal by participant), may also be considered for participation in the sub-study.

- The sub-study evaluation period will start from the time of participant withdrawal from study 219516 and will last for up to 6 months of follow-up post withdrawal to permit additional efficacy and safety data collection on subsequent ART regimen(s). This will provide a more complete dataset to further understand the study results from 219516 and inform the scientific community.

### 6.7.1. Sub-study objectives and endpoints

**Table 26 Sub-study Objectives and Endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Exploratory** | |
| CCI [redacted] | |

### 6.7.2. Sub-study design

- This is an optional, observational, sub-study that will aim to enrol participants who withdraw from study 219516, to permit continued data collection related to virologic response to subsequent ART regimens through 6 months of follow-up post withdrawal from study 219516.
- Participants are considered eligible for inclusion in the sub-study if they:
- Withdraw from study 219516 due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria met as defined under any protocol amendment, lack of efficacy).
- Withdraw from study 219516 due to non-virologic concerns (e.g., AE/SAE, withdrawal by participant) and have been impacted by virologic management related concerns (i.e., viral load elevations) at any point in study prior to withdrawal.
- Participants who have already been withdrawn from study 219516 due to virologic criteria prior to the implementation of Protocol Amendment 03 and this sub-study should also be considered for inclusion in the sub-study retrospectively.
- All participants must sign a separate sub-study ICF to be considered eligible.

- Since this sub-study is an observational study of participants who have withdrawn from the main study, the 219516 protocol-specified withdrawal and stopping criteria are not applicable. Participants may withdraw consent for the sub-study at any time. Participants are considered to have completed the sub-study at the 6 month review or when there is no additional data expected for the participant.

## 6.7.3. Statistical Analyses

### 6.7.3.1. General Considerations

- Analysis of the endpoints listed in Section 6.7.1 will be performed after all participants complete end of sub-study follow-up or prematurely discontinue from the sub-study. Further additional analyses may be performed to support regulatory activities, business planning, publication, or other purposes.
- An ad-hoc analysis may be performed on consented sub-study participants to support the week 48 and week 96 reporting.
- No data values will be imputed for missing data.

### 6.7.3.2. Definition of endpoints

Definition of endpoints is detailed in Table 27 .

### 6.7.3.3. Main analytical approach

- The frequency and percentage of participants with HIV-1 RNA <50 c/mL, 50- <200 c/mL and ≥200 c/mL will be summarized including 95% Clopper-Pearson exact confidence intervals.
- 
- All analyses in Table 27 will comprise of descriptive statistics only and all other data will be available in the RAPIDO data viewer.

#### *6.7.3.3.1. Statistical Analyses/Methods*

The table below provides an overview of the sub-study analyses.

**Table 27 Overview of Planned Sub-Study Analyses**

| Endpoints | Frequency and Percentages | | |
|---|---|---|---|
| | Summary | | Individual |
| | T | F | L |
| **HIV RNA** | | | |
| Proportion of Participants with plasma HIV RNA by category[1] and visit | Y | | |

| Endpoints | Frequency and Percentages | | |
|---|---|---|---|
| | Summary | | Individual |
| | T | F | L |
| **Description of subsequent ART regime** | | | |
| Summary of ART regimes | Y | | |
| **Describe reasons for switching from subsequent regimen and reasons for virologic failure** | | | |
| Summary of reasons for switch (if subsequent regimen is changed) | Y | | |
| Summary of reasons for virologic failure | Y | | |
| Summary of AEs leading to ART discontinuation | Y | | |
| Summary of SAEs leading to ART discontinuation | Y | | |
| Death leading to ART discontinuation | | | Y |

[1] Category consists of <50 c/ML, 50 – 200 c/mL, >200 c/mL.

- AE, SAEs, HIV genotypic resistance, pregnancy, concomitant medication and intercurrent illnesses will be available in the RAPIDO data viewer.

## 6.8. Appendix 8 Abbreviations

| | |
|---|---|
| 3TC | Lamivudine, EPIVIR |
| ABC | Abacavir, ZIAGEN |
| AE | Adverse event |
| AIDS | Acquired immune deficiency syndrome |
| ALT | Alanine aminotransferase |
| Anti-HBc | Hepatitis B core Antibody |
| ARV | Antiretroviral |
| ART | Antiretroviral therapy |

| | |
|---|---|
| ATV/r | Atazanavir/ritonavir |
| AST | Aspartate aminotransferase |
| BIC | Bictegravir |
| BMI | Body Mass Index |
| c/mL | Copies/milliliter |
| CD | Cluster of Differentiation |
| CDC | Centers for Disease Control and Prevention |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| C-SSRS | Columbia Suicidality Severity Rating Scale |
| CI | Confidence interval |
| ConART | Concomitant ART therapy |
| CoEQ | Control of Eating Questionnaire |
| CV | Cardiovascular |
| CVD | Cardiovascular Disease |
| CVW | Confirmed Virologic Withdrawal |
| DAIDS | Division of Acquired Immune deficiency Syndrome |
| DDI | Drug Drug Interaction |
| DNA | Deoxyribonucleic acid |
| DRV | Darunavir |
| DTG | Dolutegravir, TIVICAY |
| DXA | Dual-X-absorptiometry |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |

| | |
|---|---|
| eC-SSRS | Electronic Columbia Suicidality Severity Rating Scale |
| EFV | Efavirenz |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ETR | Etravirine |
| EU | European Union |
| EVG | Elvitegravir |
| FDA | Food and Drug Administration |
| FDC | Fixed-dose combination |
| FTC | Emtricitabine |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration rate |
| GGT | Gamma-glutamyl transferase |
| GSK | GlaxoSmithKline |
| HbA1c | Glycated hemoglobin |
| HBsAb | Hepatitis B surface Antibody |
| HBsAg | Hepatitis B surface Antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HDL | High density lipoprotein |
| HIV | Human immunodeficiency virus |
| HIV TSQ | HIV treatment satisfaction questionnaire |
| HOMA-IR | Homeostasis model of assessment of insulin resistance |
| ICH | International Council on Harmonization |
| IDF | International Diabetes Foundation |

| | |
|---|---|
| IgM | Immunoglobulin M |
| IN | Integrase |
| INSTI | Integrase strand transfer inhibitor |
| INR | International normalized ratio |
| IP | Investigational Product |
| LDL | Low density lipoprotein |
| LLN | Lower Limit of Normal |
| LPV | Lopinavir |
| MCv | Mean corpuscular volume |
| MedDRA | Medical dictionary for regulatory activities |
| Mg | Milligram |
| Mg/dL | Milligram per deciliter |
| MRS | Menopause Rating Scale |
| NADES | Non-Acquired Immune-Deficiency Syndrome (AIDS)-Defining Events |
| NAFLD | Non-alcoholic fatty liver disease |
| NFS | NAFLD fibrosis score |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |
| NRTI | Nucleoside reverse transcriptase inhibitor |
| OC | Observed Case |
| PBMC | Peripheral Blood Mononuclear Cell |
| PI | Principal Investigator |
| PP | Per-protocol |
| PPD | Pharmaceutical Product Development |
| PR | Protease |

| | |
|---|---|
| PSS | Phenotypic Susceptibility Scores |
| PSSf | Phenotypic Susceptibility Scores with Full Sensitivity Only |
| PSSp | Phenotypic Susceptibility Scores with Partial Sensitivity Included |
| PSRAE | Possible suicidality-related adverse event |
| PT | Preferred term |
| PVW | Precautionary Virologic Withdrawal |
| QOL | Quality of Life |
| QTc | Corrected QT interval |
| RNA | Ribonucleic acid |
| RPR | Rapid plasma reagin |
| RT | Reverse transcriptase |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SOC | System organ class |
| SoA | Schedule of activities |
| SRM | Study Reference Manual |
| SVW | Suspected Virologic Withdrawal |
| TAF | Tenofovir alafenamide |
| TRDF | Treatment Related Discontinuation = Failure |
| TSQ | Treatment Satisfaction Questionnaire |
| ULN | Upper limit of normal |
| US | United States |
| WHOQOL | World Health Organization Quality of Life. |

# 7. REFERENCES

Cahn P, Sierra Madero J, Arribas JR et al. Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy - naive adults with HIV-1 infection. AIDS. 2022 ;36(1):39-48.

Clinical Review Report: Cabotegravir Tablets, Cabotegravir Extended-Release Injectable Suspension, and Rilpivirine Extended-Release Injectable Suspension (Vocabria, Cabenuva): (ViiV Healthcare ULC): Indication: HIV-1 infection [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Sep. Appendix 4, Description and Appraisal of Outcome Measures. Available at: https://www.ncbi.nlm.nih.gov/books/NBK566695/.

D'Agostino R.B., Vasan R.S., Pencina M.J., Wolf P.A., Cobain M., Massaro J.M. Kannel W.B. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Epidemiology. 2008; 117:743-753.

Dalton M, Finlayson G, Hill A, Blundell J. Preliminary validation and principal components analysis of the Control of Eating Questionnaire (CoEQ) for the experience of food craving. Eur J Clin Nutr. 2015;69:1313-1317.

Dalton M, Finlayson G, Walsh B, Halseth AE, Duarte C, Blundell JE. Early improvement in food cravings are associated with long-term weight loss success in a large clinical sample. Int J Obes (Lond). 2017 Aug;41(8):1232-1236.

Delgado C, Baweja M, Crews DC et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. American Journal of Kidney Diseases; 2022, Volume 79, Issue 2, Pages 268-288

Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Sep 2022. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines Accessed 27 November 2022.

Department of Health and Human Services (DHHS). Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Updated 31 January 2023. Available at: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/. Accessed: 24 April 2023.

Dolutegravir/3TC (Dovato) Product Information. January 2023 or the most current version.

European AIDS Clinical Society (EACS) Guidelines for the clinical management and treatment of HIV Infected Adults in Europe. Version 11.1, October 2022. Available at: http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf. Accessed December 2, 2022.

European Medicines Agency (EMA). Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic. Version 1 March 2020(a).

European Medicines Agency (EMA). Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. 25 March 2020(b).

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

Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG; DAD study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil. 2010 Oct;17(5):491-501.

Grundy S.M., et al. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285

GSK Document Number RPS-CLIN-044825: Clinical Investigator's Brochure for GSK1349572 (Dolutegravir) Version 16. October 2022 or the most current version.

Kanters S, Renaud F, Rangaraj A et al. Evidence synthesis evaluating body weight gain among people treating HIV with antiretroviral therapy - a systematic literature review and network meta-analysis. EClinicalMedicine. 2022; 48:101412.

Liu TF, Shafer RW. Web Resources for HIV type 1 Genotypic-Resistance Test Interpretation. *Clin Infect Dis*. 2006;42 (11):1608-1618.

Llibre JM, Brites C, Cheng CY et al. Efficacy and Safety of Switching to the 2-Drug Regimen Dolutegravir/Lamivudine Versus Continuing a 3- or 4-Drug Regimen for Maintaining Virologic Suppression in Adults Living With HIV-1: Week 48 Results From the Phase 3, Non-inferiority SALSA Randomized Trial. Clin Infect Dis. 2022 Mar 2:ciac130. doi: 10.1093/cid/ciac130. Epub ahead of print.

Mallon PWG, Brunet L, Fusco JS et al. Lipid Changes After Switch From TDF to TAF in the OPERA Cohort: LDL Cholesterol and Triglycerides. Open Forum Infect Dis. 2021 Dec 8;9(1):ofab621.

Nery MW, Martelli CM, Silveira EA, de Sousa CA, Falco Mde O, de Castro Ade C, Esper JT, Souza LC, Turchi MD. Cardiovascular risk assessment: a comparison of the Framingham, PROCAM, and DAD equations in HIV-infected persons. ScientificWorldJournal. 2013 Oct 21;2013:969281.

Osiyemi O, De Wit S, Ajana F et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Versus Continuing a Tenofovir Alafenamide-Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human

Immunodeficiency Virus Type 1: Results Through Week 144 From the Phase 3, Noninferiority TANGO Randomized Trial. Clin Infect Dis. 2022 ;75(6):975-986

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

Sánchez-GarcíaA, Rodríguez-Gutiérrez R, Mancillas-Adame L, González-Nava V, Díaz González-Colmenero A, Solis RC, Álvarez-Villalobos NA, González-González JG. Diagnostic Accuracy of the Triglyceride and Glucose Index for Insulin Resistance: A Systematic Review. Int J Endocrinol. 2020 Mar 10;2020:4678526.

van Wyk J, Ajana F, Bisshop F et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose 2-Drug Regimen vs Continuing a Tenofovir Alafenamide-Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Phase 3, Randomized, Noninferiority TANGO Study. Clin Infect Dis. 2020 Nov 5;71(8):1920-1929.

Wensing AM, Calvez V, Ceccherini-Silberstein F et al. 2022 update of the drug resistance mutations in HIV-1. Top Antivir Med. 2022 ;30(4):559-574.

Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb. 2005;12(6):295-300. doi: 10.5551/jat.12.295. PMID: 16394610.

# Analysis Outline

| | | | |
|---|---|---|---|
| **Protocol ID / alias or Master Study ID:** | GSK3515864/219516 | | |
| **Date of Request:** | 23SEP2024 | **Request ID:** | NA |

## TABLE OF CONTENTS

## 1. Request information

| | |
|---|---|
| **Requestor:** | PPD |
| **Coordinating authors:** | PPD, Statistics Leader<br>PPD, Principal Statistician |
| **Scope of request:** | The purpose of this analysis outline is to compare the original HIV-1 RNA results and the retest values and assess all available VL data to understand the impact on study interpretation and assess robustness of results to support interpretation for the HIV community. |
| **Target date for distribution:** | Week 48 SAC: 11APRIL2025 |
| **Distribution list for results:** | Project Team |
| **GSK asset description(s):** | GSK3515864 |
| **Anonymisation required?** | No |
| **Database Lock Date:** | Week 48 DBL: 02APRIL2025 |
| **Project Statistician approver:** | PPD, Statistics Leader |

## 2. Rationale

The EYEWITNESS study (219516) has recently reported an unexpected increase in HIV-1 RNA levels, specifically within the low level range of VL 50-200 copies/mL. The HIV-1 RNA data with increased occurrences of increased c/mL viral load levels were generated by the PPD central laboratory using the Roche Cobas® 6800 HIV-1 RNA assay. This has led to a larger than anticipated number of study participants meeting the protocol-defined criteria for virologic management and withdrawal in comparison to previous pivotal DTG/3TC stable switch studies, namely 204862 (TANGO) and 208090 (SALSA), which employed the Abbott RealTime HIV-1 assay at Q2 central laboratory for their investigations.

Further, the virologic management and withdrawal criteria included in the EYEWITNESS study protocol amendment 02 and previous versions are conservative and aligned with ViiV historic 2-drug regimen study criteria in stable suppressed switch populations. Combined, the inclusion of this conservative virologic management criteria in the study protocol and the introduction of a more sensitive viral load assay in the study increases the risk of clinically unnecessary virologic withdrawals and participant retesting burden.

As a result, the protocol was amended to protocol amendment 3 (PA 03) to remove the Precautionary Virologic Withdrawal (PVW) criteria, which required participant withdrawal based on a maximum of three consecutive low-level viral loads between 50 and 200 c/mL (per section 7.1.2 of PA 02) and modify the CVW criteria, which required participant withdrawal based on a viral load ≥200 c/mL preceded by a viral load ≥50 c/mL (per Section 7.1.2 of PA 02), to withdrawal after two consecutive viral loads ≥200 c/mL. This will better align

participant virologic management in the study with current clinical practice and guideline recommendations.

These surprising observations have instigated extensive targeted retesting of HIV-1 RNA samples by PPD GCL on both Roche and Abbott, as well as a comparisons to local HIV-1 RNA labs (on varying assays) where available and a thorough review of the handling and processing of these samples at both the site level and at PPD central lab. The aim of this retesting and review is to provide a solid foundation for further investigations into these unexpected findings.

This supplementary analysis plan will be used to supplement the Week 48 interim analysis SAP which proposed analysis of the Roche assay data only.

The primary objective of this supplementary analysis plan is to evaluate the results of the HIV-1 RNA retests. This will involve comparing the retest results with those from other assays, local laboratory results, and the original HIV-1 RNA results. Additionally, all available VL data, including information on sample handling and processing, will be assessed.

An Abbott assay first approach in analyzing HIV-1 RNA results will be utilized in the primary interpretation of the study. The Abbott testing will allow for a consistent approach across DTG/3TC studies, an important context for interpretation in this single arm study where the Roche Cobas® assay is reporting increased blip rates and variability.

Another goal of this analysis is to gain a deeper understanding of the impact these retest findings have on the interpretation of the study. It will also help assess the robustness of the results, providing valuable insights into the reliability and validity of the findings.

For a comprehensive understanding of the overall analysis plan for this study, as outlined in the protocol, please refer to the main Statistical Analysis Plan (SAP) and the Study protocol.

# 3. Description of required analysis

## 3.1. Objectives

These objectives will help us interpret the study using an Abbott assay first approach and investigate if the original per-protocol VL results analyzed using Roche assay are in agreement with retested results from stored samples using Roche assay, Abbott assay and local lab VL results.

The objectives and endpoints for this supplementary analysis include;

| Objectives | Endpoints | Clarity on Intent of analysis |
|---|---|---|
| Primary | | |
| • To evaluate the maintenance of virologic suppression of DTG/3TC at Week 48 post switch from BIC/FTC/TAF using an Abbott assay first approach | • Participants with plasma HIV-1 RNA ≥50 copies/mL (Snapshot algorithm) at Week 48 | • This will provide the primary interpretation of study |
| Secondary | | |
| • Explore the impact of the Abbott and Roche Cobas® 6800 assays on Snapshot | • Participants with plasma HIV-1 RNA ≥50 copies/mL (Snapshot algorithm) at Week 48 | • To investigate the difference between the assays on the primary endpoint of the study |
| • To compare all paired samples of Roche Cobas® 6800 HIV-1 RNA assay and Abbott RealTime HIV-1 Viral Load assay overtime | • Absolute values and differences in HIV-1 RNA/log10 values overtime<br>• Participants with any paired HIV-1 RNA values with differences <0.3log10, ≥0.3log10 - <0.5log10 and ≥0.5log10<br>• Bland – Altman Analysis of agreement in HIV-1 RNA values over time<br>• Participants with <50, ≥50 – 200, ≥200 copies/mL by assay | • Summary of VL over time will be presented side by side to show any trends/agreement between VL tests<br>• Summary of VL by thresholds of <0.3log10, ≥0.3log10 - <0.5log10 and ≥0.5log10will highlight if VL differences between tests represent clinically important changes as per current guidelines on the precision of PCR tests.<br>• The Bland-Altman analysis will help assess any differences between tests measurements and observe if these are symmetrically distributed and no indication of serious heteroscedasticity |

| Objectives | Endpoints | Clarity on Intent of analysis |
|---|---|---|
| | | – i.e. no marked increase/decrease in variance of differences with increasing VL.<br>• Summary of participants by VL category will provide concordance/discordance between assay |
| Tertiary | | |
| Explore the impact of sample handling on the primary endpoint | • Participants with plasma HIV-1 RNA ≥50 copies/mL ( Modified Snapshot algorithm) at Week 48 | • To investigate whether sample handling impacted the primary endpoint of the study |
| To evaluate HIV-1 RNA sample handling and processing at the site level and at central laboratory using information from sample tracker | • Time-lag between date of HIV-1 RNA sample collection and date of Laboratory analysis<br>• Participants with documented unable to perform (UTP) plasma HIV-1 RNA samples overtime | • Time-lag analysis will investigate relationship between VL results and duration between sample collection and results availability.<br>• Sample handling and processing may significantly impact VL results if not handled per protocol . summary of participants with UTP will provide valuable information and reliability of these VL elevations |
| To evaluate the likelihood of observing virologic failures in EYEWITNESS given prior data | • The probability of observing virologic failures we have in EYEWITNESS given prior data from SALSA and TANGO | • To quantify how the probability of observing virologic failures in EYEWINTESS given historical data |

## 3.2. Estimands

The primary approach for interpretation estimand aims to evaluate virological failure with DTG/3TC at Week 48 post-switch from BIC/FTC/TAF in virologically suppressed people living with HIV of at least 50 years of age.

**Table 2 Virological Failure Estimand**

| | |
|---|---|
| Population | People living with HIV of at least 50 years of age who are virologically suppressed on Biktarvy (BIC/FTC/TAF) |
| Treatment | DTG/3TC FDC (Dovato) administered once daily over 48 weeks post-switch from Biktarvy (BIC/FTC/TAF) administered orally once daily |
| Intercurrent Events | Study treatment discontinuation due to lack of efficacy or other reasons that impact the viral load outcome: Composite strategy.<br>*Rationale*: The presence of missing data due to lack of efficacy or discontinuation for other reasons on the primary approach for interpretation is adequately accounted for in the Abbott-first Snapshot Algorithm which frames the outcome around these events. Thus, discontinuation prior to week 48 due to the Roche assay result is accounted for.<br>See Section 4.3.1 for full details on Snapshot Algorithm. |
| Endpoint | Participant with virologic failure (plasma HIV-1 RNA ≥ 50 c/mL as per Snapshot algorithm at 48 weeks) |
| Summary measures | Number and percentage of participants with virologic failure (plasma HIV-1 RNA ≥ 50 c/mL as per Abbott-first Snapshot algorithm at 48 weeks), within group 95% confidence interval using Exact (e.g., Clopper-Pearson) methodology |

## 3.3. Analysis Sets

| Analysis Set | Definition/Criteria | Analyses Evaluated |
|---|---|---|
| Full Analysis Set (FAS) | Please see main study SAP for definition | • All non-paired analyses |
| FAS Abbott-Roche Paired (FAS-AR Paired) | Participants in the FAS population with availability of a paired set of HIV-1 RNA results using the Abbott assay | • All paired analyses using Abbott and Roche assays |

# 4. Statistical Analyses

## 4.1. General Considerations

Unless otherwise stated, please refer to the main Statistical Analysis Plan for all general statistical considerations, data handling, analysis windows and display conventions.

## 4.2. Analysis Timepoint

In addition to nominal visit defined in the main SAP (Table 22), some analysis will be summarized by calendar month. Calendar month will be defined for each year

starting from first subject first visit to last subject last visit using date of assessment.

## 4.3. Modified Snapshot Algorithm

### 4.3.1. Primary Approach for Interpretation

The primary approach for interpretation of the EYEWITNESS study at week 48 will employ the modified snapshot algorithm (as described in Section **Error! Reference source not found.**) and take an 'Abbott first' approach.

For Abbott first approach, the selection of the HIV1-RNA result for the week 48 snapshot algorithm will be as follows:

- If an Abbott sample is available and in window, this result will be used;
- If a participant withdraws before Week 48, the last available Abbott result will be used;
- Otherwise, use the Roche sample[1].

A participant's virology response and reason at Week 48 will be categorized as below:

- HIV1-RNA < 50 copies/mL
- HIV1-RNA ≥ 50 copies/mL
    - Based on Abbott
        - Data in window not below 50
        - Discontinued for lack of efficacy
        - Discontinued for other reason while not below threshold
    - Change in background therapyBased on Roche
        - Data in window not below 50
        - Discontinued for lack of efficacy
        - Discontinued for other reason while not below threshold
        - Change in background therapy
- No Virologic Data at Week 48 Window
    - Discontinued study due to AE or death
    - On study but missing data in window
    - Based on Abbott
        - Discontinued study for other reasons
    - Based on Roche

[1] Note that:

For failures/withdrawals based on Roche testing for Subject Management, the Abbott sample will be used if available to determine category in the snapshot algorithm, otherwise, the Roche sample will be used.

For failures for non viral-related reasons, the Roche sample will be used.

- Discontinued study for other reasons.

### 4.3.2. Roche first approach

The analysis approach outlined in Section 4.3.1 will be repeated using a Roche first approach if more than 5% of participants have an Abbott result but no Roche result.

### 4.3.3. Concordance between Roche-only and Abbott-first outcomes

A table displaying the concordance between the Roche-only and Abbott-first snapshot outcomes will be presented with the categories, HIV-1 RNA <50 c/mL, HIV-1 RNA ≥50c/mL and no virologic data in window.

Percentage of <50 c/mL on the re-test visit with initial Roche ≥50 c/mL – by visit and by initial viral load category will be presented. This will be repeated by initial Roche category: ≥50-200, ≥200.

### 4.3.4. Accounting for sample handling and processing

The analyses outlined in Sections 4.3.1 and 4.3.2 will be repeated re-categorizing participants with PDs related to sample handling and processing (SHP). A participant will be re-categorized as SHP issue in Window† if :

- Their week 48 HIV-1 RNA sample has a PD related to SHP and:
  - their RNA result is ≥ 50 copies/mL or
  - they have no virological data within the Week 48 window.

A summary of duration of date of HIV-1 RNA central lab original Roche sample collection to laboratory analysis will be produced by calendar month and overall. Time between sample duration will be summarized descriptively and also by categories; <2 days, 2- <5 days, 5- <7, 7- <14, ≥14 days.

† Note: PDs with 'SHP issue in window' include any sample handling and processing issue recorded for any HIV-1 RNA, Virology Plasma or Whole Blood Aliquots within analysis window and documented in the sample tracking data as 'Unable to Perform (UTP), outside stability, missing samples, or expired tubes.

## 4.4. Differences in HIV-1 RNA

All analyses in this Section will be summarized using the FAS-AR population with the exception of the percentage of <50c/mL on the retest visit summary, which will be summarized using the FAS population.

Summaries of participants with any paired HIV-1 RNA values with differences <0.3log10, ≥0.3log10 - <0.5log10 and ≥0.5log10 will be presented.

Contingency table summaries of participants with any HIV-1 RNA values <50, ≥50 – 200, ≥200 copies/mL will be presented by assay.

## 4.5. Bland-Altman analysis

To quantify the level of agreement between HIV-1 RNA results from the Roche and Abbott samples, a Bland-Altman plot of the two results will be produced and presented by study visits. The plot will display the mean of original and retested log-transformed HIV-1 RNA values (X-axis) vs the differences in the Roche and Abbott log-transformed HIV-1 RNA values (Y-axis), the following reference values will be included in the plot;

- Mean Differences (bias between two measurements)
- 95% confidence limits of Mean Differences

A histogram to display the distribution differences in the Roche and Abbott log-transformed HIV-1 RNA values will be produced to assess the assumption that the differences follow a normal distribution.

## 4.6. Sample Handling and Processing

HIV-1 RNA stability in the whole blood or plasma can be impacted significantly by various factors during sample management at sites, transportation and at central laboratory. These factors may be caused by temperature excursion, sample quantity, duration of storage, processing time delays, transportation condition etc. For this study, sample tracking data will be used to identify subjects with sample status recorded as 'Unable to Perform (UTP), outside stability, missing samples, or expired tubes at each visit and recorded as protocol deviation. This information will be summarized by number per participant, site level, overtime and overall to quantify its impact on the study results.

Summary of duration of date of HIV-1 RNA Original Roche sample collection to date of laboratory analysis will be presented overall and by calendar month.

## 4.7. Subgroup Analyses

The subgroups specified below may be explored for this analysis. Additional subgroups of clinical interest may also be considered.

| Subgroup Category | Subgroup variables and levels |
|---|---|
| Demographic and Baseline Characteristics | • Age (years)[1]<br>  ○ <65, ≥65<br>• Site<br>• Region[1]<br>  ○ North America, Europe |

| Subgroup Category | Subgroup variables and levels |
|---|---|
| | • Baseline CD4+ cell count (cells/mm$^3$)<br>  ○ <350, 350 to <500, ≥500<br>• Baseline HIV-1 RNA[2]<br>  ○ <50 c/mL, ≥50c/mL |
| Comorbidities at Baseline | • Relevant Comorbidities at Baseline[3]<br>  ○ 0, 1, 2, 3, >3 |
| **NOTE:**<br>[1]See main SAP section 6.1.3. for additional details on demographic and baseline characteristics.<br>[2]This is based on the Roche baseline result and is reflecting the variability. This subgroup is likely to uninformative due to the trial population being stable prior switch.<br>[3]Relevant comorbidities include cardiovascular, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders, mental health issues (particularly depression and anxiety disorders), sexual dysfunction and age-related changes such as menopause. | |

## 4.8. Prediction Analysis

An analysis of how likely the number virological failure observed in EYEWITNESS based on prior data in SALSA and TANGO will be performed in consultation with the Statistics and Data Science Innovation Hub (SDS-IH). Details of the analysis will be developed in a supplementary plan that will appended to this SAP.