Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan Amendment 3 for ViiV Healthcare-sponsored study 205543 (GEMINI-II): A Phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults
Compound Number	:	GSK1349572 + GR109714 (GSK3515864)
Effective Date	:	18 Jul 2022

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol 205543 (GEMINI-II).
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables for reporting efforts up to Week 148.
- The planned (futility) and the event-triggered (CVW reviews) IDMC analyses are not covered in this RAP. Please refer to SF_1 00 Reporting and Analysis Plan (RAP)_D3 IDMC_204861_205543_13th_Dec 2016.
- This version of the RAP amendment 3 (to the originally approved RAP dated 04-JAN-2018 and RAP amendment 1 dated 08-APR-2019 and RAP amendment 2 dated 05-MAY-2020) is to provide details on the Final End of Study (EOS) analysis.

RAP Authors:

Approver	Date
PPD Director, Biostatistics Parexel FSP	12-JUL-2022

RAP Team Review confirmations
(Method: E-mail)

Approver	Date
PPD Director, Clinical Science Lead, ViiV Healthcare	06-JUL-2022
PPD Medicines Development Lead, ViiV Healthcare, Global Medical Strategy team	05-JUL-2022
PPD Medical Director, Safety and Medical Governance, GSK	06-JUL-2022
PPD Clinical Development Director, ViiV Healthcare, CSMO	05-JUL-2022
PPD Clinical Development Investigator, ViiV Healthcare	06-JUL-2022
PPD Clinical Development Lead, ViiV Healthcare	06-JUL-2022
PPD Data Management Quality Lead, GSK	08-JUL-2022
PPD Study Delivery Lead, GSK	12-JUL-2022

Clinical Statistics and Clinical Programming Line Approvals
(Method: Pharma TMF eSignature)

Approver	Date
PPD Principal Statistician, GSK	18 Jul 2022
PPD Programming Director, Clinical Programming, GSK	18 Jul 2022

The main changes included in RAP Amendment 3 are listed in Section 10.16 Appendix 16 – End of Study Analysis

The main changes included in RAP Amendment 2 are

The following few efficacy tables, safety tables, figures and listings are removed from Week 144/148 analyses. Please see Appendix 17 for details.

- Additional category subgroup analysis of baseline plasma HIV-1 RNA and CD4+ cell count - for study outcomes (< 50 c/mL) and for proportion of subjects with plasma HIV-1 RNA < 50 c/mL;
- Summary of adverse events by system organ class, maximum toxicity and subgroups;
- Summary of adverse events leading to permanent discontinuation of study treatment or withdrawal from study by subgroups;
- Summary of total duration of adverse events of special interests for Anxiety, Depression, Drug Hypersensitivity, Insomnia, Nightmare/Abnormal Dreams, Rash, Suicidality and Self-Injury;
- Summary and analysis of change from baseline in bone/renal biomarkers and lipids by subgroups;
- Summary of changes in TC/HDL ratio, NCEP lipid from baseline category to maximum (minimum for HDL) post-baseline category;
- Bar chart of TC/HDL ratio, NCEP lipids at baseline vs. maximum (minimum for HDL) post baseline;
- Summary and listing of subjects meeting hepatobiliary abnormality criteria - all post-baseline abnormalities;
- Summary of weight and BMI by visit;

Explanation of Week 144 analysis non-inferiority margin added;

Clarification for Columbia Suicide Severity Rating Scale endpoint derivation added;

Derivation for analysis windowing edited and added to account for scheduled week 148 visit;

For week 148 analysis, a cut-off flag for data exclusion will be derived as:

- Any assessments done after the upper bound study day 1050 (for parameter without scheduled visit at week 148) or 1078 (for event data and parameters with scheduled visit at week 148) will be excluded from week 148 analysis (tables and figures only), all data will be listed & also plotted in the individual subject plot.

The main changes included in RAP Amendment 1 are:

In accordance with the new CDC HIV staging categories, only Stage 3 HIV Associated Conditions were listed.

Statistical Analysis of Kaplan-Meier Estimates of Time to Viral Suppression (including figures) will be run Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups

Statistical Analysis of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal at Week X - Efficacy Related Discontinuation = Failure will be run Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups

In Time to Viral Suppression Analysis Subjects who withdraw for any reason without being suppressed during on treatment will be censored at earliest of (day of study discontinuation, day of withdrawal visit, day of treatment discontinuation) instead of withdrawal.

Due to the nature of the data, the eCSSRS summaries were analysed using nominal visits instead of analysis visits based on visit windowing.

Two additional renal biomarkers were analysed: Urine Beta-2 Microglobulin/Urine Creatinine, Urine Retinol Binding Protein/Urine Creatinine and two biomarkers were removed: Urine Beta-2 Microglobulin and Urine Retinol Binding Protein.

Summary of Maximum Post-Baseline Emergent Chemistry Toxicities was updated to remove the overall summaries for calcium, glucose, potassium and sodium, and were instead summarized by 'hyper' and 'hypo' categories.

For AE data, the lag time of 1 day is removed for 'On-treatment' derivation.

New explanation added to 10.6.1 Week 24/48/96/144 cut-off date section how to check if the PD occurred prior or at week X viral load date (used for snapshot algorithm)

Two additional subgroups were analysed: Age (<50, vs ≥50) and Race (White vs. Non-White).

Clarification added stating that Multiple imputation (MAR) analyses will be run at week 24 and 48 only. No MAR analyses after week 48 will be performed. Mixed Model Repeated Measures (MMRM) analysis will be considered as the main analyses onwards.

Clarification added stating that certain subgroups will be summarised and analysed for lipids and certain renal biomarkers after week 48.

The following additional tables were included:

Number of Subjects Attending Nominal and Actual Analysis Visits

Summary of changes in total cholesterol/HDL ratio Baseline category to Week X

Summary of AEs leading to permanent discontinuation of study treatment or withdrawal from study by maximum grade

Summary of drug-related Grade 2-5 AEs

Summary of Subjects Meeting Hepatobiliary Abnormality Criteria - All Post- Baseline Abnormalities

Subjects Meeting Hepatobiliary Abnormality Criteria - All Post-Baseline Abnormalities

Plot of Common (>=2%) Grade 2-5 Adverse Events and Relative Risk

Plot of Common (>=2%) Drug-Related Adverse Events and Relative Risk

Plot of Adverse Events Categories and Relative Risk

Summary of absolute values of fasting lipids by visit

Summary of CD4+ Cell Count (cells/mm3) by Visit

Summary of weight (kg) by Visit

Summary of Change from Baseline in weight (kg) by Visit

Summary of BMI (kg/m2) by Visit

Summary of Change from Baseline in BMI (kg/m2) by Visit

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X by Subgroups - Snapshot Analysis – Per Protocol population

Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL at Week X - Snapshot Analysis - ITT-E

Summary of Study Outcomes (<40 c/mL) at Week X - Snapshot Analysis - ITT-E

Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL by Visit – Snapshot Analysis

Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL at Week X by Subgroups - Snapshot Analysis - ITT-E

Summary of Study Outcomes (<50 c/mL) at Week X by Baseline Plasma HIV-1 RNA and CD4+ Cell Count - Snapshot Analysis

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X by Baseline Plasma HIV-1 RNA and CD4+ Cell Count - Snapshot Analysis – ITTE

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X by Baseline Plasma HIV-1 RNA and CD4+ Cell Count - Snapshot Analysis - PP

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP describes the planned analyses and outputs required for the Clinical Study Reports for protocols 204861 (GEMINI-I) and 205543 (GEMINI-II). • The planned (futility) and the event-triggered (CVW reviews) IDMC analyses are not covered in this RAP. Please refer to SF_1 00 Reporting and Analysis Plan (RAP)_D3 IDMC_204861_205543_13th_Dec 2016.
Protocol	• This RAP is based on the protocol amendment 2 of study 205543 (Dated: 14-JUN-2018, GSK Document No.: 2015N263962_02) and eCRF Version 10.0 (Dated: 20-APR-2020).
Primary Objective	• To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjects.
Primary Endpoint	• Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm for the intent-to-treat exposed (ITT-E) population.
Study Design	• 205543 and 204861 are two identical Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority studies. • Each sister study will be conducted in approximately 700 (350 subjects per arm) HIV-1 infected ART-naïve adults with screening plasma HIV-1 RNA of 1,000 to ≤ 500,000 c/mL. • Subjects will be randomized 1:1 to receive a two-drug regimen of DTG plus 3TC once daily or the three-drug regimen of DTG plus the FDC tablet of TDF/FTC once daily. Randomization will be stratified by screening plasma HIV-1 RNA (≤ or > 100,000 c/mL) and screening CD4+ cell count (≤ or > 200 cells/mm3). • Both studies will comprise a 28-day screening phase (which may be extended to 35 days to allow receipt of all screening assessment results), a double-blind randomised phase (96 weeks), an open-label randomised phase (between Wee 96 and Week 148) and a continuation phase. • No dose reductions, modifications in dosage, or changes in the frequency of dosing of any components of each regimen will be allowed in these studies.
Planned Analyses	• The primary analysis at Week 48 will take place after the last subject has had their Week 48 viral load assessed, including a retest if required.

Overview	Key Elements of the RAP
	• Further interim analyses may be conducted to support regulatory submissions and publications and pricing reimbursement dossiers. In particular, the following analyses will take place: secondary analysis at Week 24 (when the last subject has had their Week 24 viral load assessed, including a retest if required), secondary analysis at Week 96 (when the last subject has had their Week 96 viral load assessed, including a retest if required) and secondary analysis at Week 144 (when the last subject has had their Week 144 viral load assessed, including a retest if required).
Analysis Populations	• The 'All subject screened' population consisting of all subjects screened, including screen-failures. • The 'Intent-to-Treat Exposed' (ITT-E) population consisting of all randomised subjects who receive at least one dose of study medication, assessed according to their randomised treatment regardless of the treatment they receive. Unless otherwise stated, the ITT-E population will be used for the efficacy analyses. • The 'Intent-to-Treat' (ITT) population comprise of all randomised subjects. Subjects will be assessed according to their randomised treatment even if no study treatment was taken or the wrong treatment was received. • The 'Per-Protocol Population' consisting of subjects in the ITT-E population with the exception of significant protocol deviators, e.g. deviations that could affect the assessment of antiviral activity. Unless otherwise stated, the PP population will be used for the sensitivity analyses of the primary efficacy endpoint. • The 'Safety' population consisting of all subjects who receive at least one dose of study medication, assessed according to their actual treatment they received. Unless otherwise stated, this population will be used for the safety analyses. • 'CVW' comprise of all subjects in the ITT-E population who have met the derived CVW criteria. • 'Viral Genotypic' comprise of all subjects in the ITT-E population who have available On-treatment genotypic resistance data. • 'Viral Phenotypic' comprise of all subjects in the ITT-E population who have available On-treatment phenotypic resistance data.
Hypothesis	• This study is designed to show that the antiviral effect of a simplified two-drug regimen of DTG plus 3TC once-daily is not inferior to a standard three-drug regimen of DTG plus TDF/FTC FDC once daily in HIV-1 infected ART-naïve adult subjects. Non-inferiority will be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -10%.

Overview	Key Elements of the RAP
Primary Analyses	• The primary endpoint will be analysed using a Cochran-Mantel-Haenszel stratified analysis, adjusting for baseline stratification factors. A point estimate and corresponding 95% confidence interval will be constructed for the adjusted difference in response rates between DTG + 3TC and DTG + TDF/FTC treatment groups.
Secondary Analyses	• Secondary analyses will be conducted for additional efficacy, safety, health outcomes, and virologic endpoints.
Sensitivity Analyses	• At Weeks 24, 48, 96, and 144, the analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population. If both analyses show non-inferiority then the hypothesis that the antiviral effect of treatment with DTG plus 3TC is superior to treatment with DTG plus TDF/FTC FDC will be tested using the same level of significance as for the tests of non-inferiority. Superiority will be declared if the lower end of the confidence internal is above 0%. The primary comparison will also be performed using the ITT population and will be compared for consistency with the results from the ITT-E and PP populations. • The time to Confirmed Virologic Withdrawal (CVW) or treatment related (TRDF)/efficacy (ERDF) related discontinuation (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy) will be calculated. This analysis censors subjects who have not met CVW criteria and are ongoing in the study, or who have discontinued for reasons other than those related to treatment/lack of efficacy. • At Week 48 a sensitivity analysis will be performed to assess whether bias was introduced by the unblinded analysis performed at Week 24. The Week 48 Snapshot results of the subjects who reached Week 48 prior to the Week 24 unblinding will be compared to the Week 48 results in the subjects who reached Week 48 after the Week 24 unblinding.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 2 of study 205543 (Dated: 14-JUN-2018, GSK Document No.: 2015N263962_02). Please note that these two studies are identical in terms of study design and analysis plan.

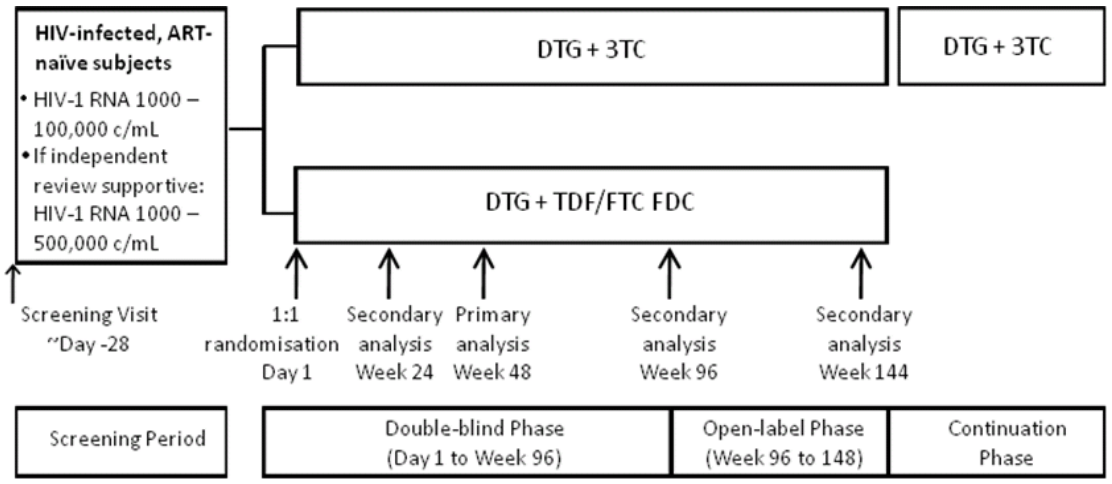
2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC FDC at 48 weeks in HIV-1-infected, ART-naïve subjects	• Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm for the intent-to-treat exposed (ITT-E) population
Secondary Objectives	**Secondary Endpoints**
• To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC FDC at 24, 96 and 144 weeks	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the FDA Snapshot algorithm for the ITT-E population
• To evaluate the antiviral activity, immunological effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC compared to DTG + TDF/FTC FDC over time	• Time to viral suppression (HIV-1 RNA <50 c/mL); • Absolute values and changes from baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144; • Incidence of disease progression (HIV associated conditions, AIDS and death).
• To assess viral resistance in subjects meeting confirmed virologic withdrawal (CVW) criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC FDC in subjects meeting CVW criteria
• To evaluate the safety and tolerability of DTG + 3TC compared to DTG + TDF/FTC FDC over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities; • Proportion of subjects who discontinue treatment due to AEs over 24, 48, 96 and 144 weeks
• To evaluate renal biomarkers (in urine and blood) and bone biomarkers (in blood) in subjects treated with DTG + 3TC compared to DTG + TDF/FTC FDC	• Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144

Objectives	Endpoints
• To evaluate the effects of DTG + 3TC on fasting lipids compared to DTG + TDF/FTC over time	• Change from Baseline in fasting lipids at Weeks 24, 48, 96, and 144; • The incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144;
• To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG + 3TC compared to DTG + TDF/FTC over time	• Proportion of subjects by patient subgroup(s) (e.g. by age, gender, Baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at Weeks 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
• To assess change in health-related quality-of-life for subjects treated with DTG plus 3TC compared to DTG + TDF/FTC	• Change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144
Exploratory Objectives	**Endpoint**
• To evaluate inflammation biomarkers in subjects treated with DTG+ 3TC compared to DTG + TDF/FTC	• Change from Baseline in inflammation biomarkers at Week 48, 96 and 144 (data will be collected at Day 1, Week 48 and 144, but results will be available for analysis at Week 96 and 144.)
• To evaluate telomere length in subjects treated with DTG + 3TC compared to DTG + TDF/FTC	• Change from Baseline in telomere length at Week 96 and 144 (telomere length results will not be available until EOS)

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority study. This study comprises a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results), a Double-blind Randomized Phase (Day 1 to Week 96), an Open-Label Randomized Phase (Week 96 to Week 148) and a Continuation Phase (Post-Week 148).
Dosing	• Patients are randomized to receive DTG (50mg) + 3TC (300mg) once daily or DTG (50mg) + TDF (300mg) / FTC (200 mg) FDC once daily
Treatment Assignment	• In each study, approximately N=700 subjects will be randomized 1:1 to DTG+3TC or DTG+TDF/FTC FDC • Stratified randomisation by Baseline HIV-1 RNA (≤ vs. >100,000c/mL) and Baseline CD4+ cell count (≤ vs. >200 cells/mm^3) • The study initially enrolled subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG + 3TC dual regimen underwent independent review (Dated: 4-NOV-2016), which was supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, and allowing recruitment to open to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL.
Interim Analyses	• Four planned analyses will be conducted to evaluate primary and secondary objectives of the protocol. Further data cuts and analyses may be conducted in order to support regulatory submissions and publications. The Week 48 analysis will be primary. No adjustment for multiplicity caused by repeated evaluation of the primary endpoint will be made as the Week 24, Week 96 and Week 144 analyses will be secondary.
Final Analysis	• A final End-of-Study analysis will be conducted when all subjects have completed the study.

2.4. Statistical Hypotheses

This study is designed to show that the antiviral effect of a simplified two-drug regimen of DTG + 3TC once-daily is non-inferior to a standard three-drug regimen of DTG + TDF/FTC FDC once daily in HIV-1 infected ART-naïve adult subjects.

Non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -10%. If r_d is the response rate on DTG + 3TC and r_f is the response rate on DTG + TDF/FTC FDC, then the hypotheses can be written as follows:

$$H_0: r_d - r_f \leq -10\% \qquad H_1: r_d - r_f > -10\%$$

2.4.1. Week 144 Statistical Hypotheses

Though the confirmatory non-inferiority test is designated at Week 48, it is planned to do non-inferiority test and report results at some other key timepoints (Weeks 24, 96 and 144) even if these analyses are exploratory in nature. For the Week 24 and 96 analysis, the same non-inferiority margin was used as specified in the protocol for the primary endpoint analysis at Week 48.

For the purpose of the Week 144 analysis, a non-inferiority margin of 12% will be used. Using a non-inferiority margin of 12%, non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -12%. If r_d is the response rate on DTG + 3TC and r_f is the response rate on DTG + TDF/FTC FDC, then the hypotheses can be written as follows:

$$H_{02}: r_d - r_f \leq -12\% \qquad H_{12}: r_d - r_f > -12\%$$

Additionally, if non-inferiority is met with this margin, non-inferiority will be assessed in a closed testing procedure against a non-inferiority margin of 10% without multiplicity adjustment.

2.4.2. Rationale for non-inferiority margin at Week 144

With longer follow-up duration it is expected to have lower response rates as more subjects withdraw from the study. Lower response rates are being associated with larger binomial variance. As such, the primary non-inferiority margin for the Week 144 analysis is 12%.

3. PLANNED ANALYSES

3.1. IDMC Interim Analyses

An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of both studies (204861 and 205543). An ad-hoc review of data by the IDMC will be triggered whenever the number of CVWs exceeds thresholds pre-specified in the IDMC charter. Further, an interim futility analysis will be performed for the IDMC to evaluate the efficacy and safety of DTG plus 3TC when approximately 50% of subjects have completed their visit at Week 24; the sponsor will remain blinded to this analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter and IDMC RAP.

3.2. Primary Analyses

The primary analysis at Week 48 will be conducted to evaluate primary and secondary objectives of the protocol.

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

1. All subjects have completed their week 48 visit as defined in the protocol, including a retest if required.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

3.3. Interim Analyses

At least three other analyses will be conducted to evaluate primary and secondary objectives of the protocol, when all subjects have completed their visits at Week 24, at Week 96, and at Week 144. Further data cuts and analyses may be conducted as necessary after Week 144 in order to support regulatory submissions and publications.

The planned analyses at Weeks 24, 96 and 144 will be performed after the completion of the same steps specified in Section 3.2.

ViiV Healthcare/GSK will unblind the study for the purpose of the Week 24 analysis; however, the PPD (except IVRS personnel), subjects and investigators will remain blinded to treatment allocation until each subject has reached their Week 96 visit.

3.4. Final Analyses

A final End-of-Study analysis will be conducted when all subjects have completed the study.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All subject screened	• Comprise of all subjects screened for inclusion in the study, including screen-failures. • This population will be based on the treatment to which the subject was randomized. Screen-failures will be categorised as "Non-randomised".	• Study Population
Randomized	• The Randomized population will consist of all subjects who are randomized in the study	• Study Population
Intent-To-Treat Exposed (ITT-E)	• Comprise of all randomized subjects who receive at least one dose of study treatment. • This population will be based on the treatment to which the subject was randomized. • Any subject who receives at least one dose of study medication and randomization number	• Study Population • Efficacy
Intent-To-Treat (ITT)	• Comprise of all randomised subjects. • Subjects will be assessed according to their randomised treatment even if no study treatment was taken or the wrong treatment was received.	• Efficacy (Sensitivity analyses)
Per-Protocol (PP)	• Comprise of all subjects of the ITT-E population who have no significant protocol deviation that could affect the assessment of antiviral activity. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Section 10.1 (Protocol Deviation Management and Definition for Per-Protocol Population).	• Efficacy (Sensitivity Analysis)

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprise of all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received.	• Safety
CVW	• Comprise of all subjects in the ITT-E population who have met the derived CVW criteria	
Viral Genotypic	• Comprise of all subjects in the ITT-E population who have available On-treatment genotypic resistance data. Assessed according to their randomised treatment regardless of the treatment they receive.	• Virology
Viral Phenotypic	• Comprise of all subjects in the ITT-E population who have available On-treatment phenotypic resistance data. Assessed according to their randomised treatment regardless of the treatment they receive.	• Virology

NOTES :

- Refer to Appendix 17: List of Data Displays which details the population to be used for each displays being generated.
- Refer to Appendix 6 which describes how CVW is derived.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important deviations which result in exclusion from the per protocol analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the ViiV-GSK 204861-205543 Study Deviation Rules Document.
    - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset. Note: It will not be possible to identify whether subjects received a different treatment to the one they were randomised to until post unblinding, hence this protocol deviation will be identified after unblinding the database.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

- There are no planned adjustments made for multiple centres in this study.
- There are no planned adjustments for multiple comparisons or multiplicity.
- There are no Pharmacokinetic and Pharmacodynamic analyses planned in this study.

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 10.2	Appendix 2: Time & Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States and Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions
Section 10.6	Appendix 6: Derived and Transformed Data
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance
Section 10.9	Appendix 9: FDA Snapshot Algorithm
Section 10.10	Appendix 10: Multicenter Studies
Section 10.11	Appendix 11: Examination of Covariates, Subgroups & Other Strata
Section 10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Section 10.13	Appendix 13: Time to Event Details
Section 10.14	Appendix 14: Q2 Creatinine Assay Accuracy Issue
Section 10.15	Appendix 15: Abbreviations & Trade Marks
Section 10.16	Appendix 16: End of Study (Final) Analysis
Section 10.17	Appendix 17: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT-E population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 17: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated	
	Table	Listing
Randomisation		
Randomisation		Y [1]
Subject Disposition		
Subjects Enrolled by Country and Site ID [2]	Y	Y
History of Rescreened Subjects[2]		Y
Reasons for Screen Failure [2]	Y	Y
Subjects for Whom the Treatment Blind was Broken		Y
Subject Disposition	Y [3,4]	
Reasons for Withdrawal by Visit	Y	Y
Study Visit Dates		Y
Populations Analysed		
Study Populations [2]	Y	Y
Protocol deviations		
Important Protocol Deviations	Y	Y
Deviations leading to exclusion from PP	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Demography		
Demographic Characteristics[5]	Y	Y
Subgroups		Y
Summary of Age Ranges	Y	
Race & Racial Combinations[6]	Y	Y
Hepatitis C Status	Y	Y
CDC Classification of HIV infection at Baseline	Y	Y
HIV Risk Factor	Y	Y
Cardiovascular Risk Assessments at Baseline	Y	Y
Distribution of Quantitative Plasma HIV-1 RNA	Y	
Distribution of CD4+ Cell Counts	Y	

Display Type	Data Display's Generated	
	Table	Listing
History of Cardiac Therapeutic Procedures		Y
Medical Conditions, Concomitant Medications & Antiretroviral Therapy		
Medical Conditions (Current and Past)	Y	Y[7]
Medical Conditions: Sub-conditions (Current/Past)	Y	
Concomitant Medications (non-ART)	Y[8]	Y[7,9]
Prior and Concomitant ART Medications		Y[7,10]
Lipid Modifying agents (Baseline and Post-Baseline)	Y	
Other		
IP Accountability [11]		Y
History of Depression and Anxiety at Baseline	Y	
Subjects attending Nominal and Actual Analysis Visits	Y	

NOTES :

- Y = Display Generated, T = Tables, L = Listings, IP = Investigational Product

1. Randomized population. One listing of subjects randomised but not treated, and one listing of planned and actual treatment strata.
2. All Subjects screened population.
3. Subject Accountability by Phase (Overall, Double Blind Phase, Open Label Phase)
4. Subjects who have not been recorded as either completing or withdrawing from the study in the respective phase will be categorized as "Ongoing at time of the analysis" for summary purposes.
5. Age, sex, ethnicity, weight, height and BMI (kg/m^2) collected at screening.
6. The five high level FDA race categories and designated Asian subcategories will be summarised along with all combinations of high level categories which exist in the data. The nine race categories collected will be summarised along with categories for mixed race. A by-subject listing of race will also be produced.
7. Repeated for subjects at sites in Mexico who experienced an adverse event, at End of Study reporting only.
8. Three separate tables, summarised by Ingredient ATC Level 1, Ingredient combinations and Combination term ATC Level 1 (EG Includes single-ingredient medications with multi-ingredient medications labelled according to the sum of their ingredients, e.g., "TYLENOL Cold and Flu" would appear as "CHLORPHENAMINE MALEATE + DEXTROMETHORPHAN HYDROBROMIDE + PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE" under the ATC headings for "Nervous System" and "Respiratory System" (the combination's ATC classifications).)
9. One listing for all concomitant medications and one listing showing the relationship between verbatim text, ingredient and ATC Level 1.
10. One listing for Prior ART, one listing for concomitant ART and one listing showing the relationship between verbatim text, ingredient, combination and ATC Level 4.
11. Dispensation information (dates and number of tablets dispensed and returned)

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

The primary efficacy analyses will be based on the "Intent-To-Treat Exposed" population, unless otherwise specified. Summaries will be presented by treatment group with no total column. Primary and secondary efficacy Tables/Figures/Listings will be performed for each reporting effort, i.e., outputs from Section 7.1.1 and Section 8.1.1 will be produced for week 24, 48, 96 and 144 analysis.

7.1.1. Overview of Planned Efficacy Analyses

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 17: List of Data Displays.

Table 3 Overview of Planned Efficacy Analyses

[Endpoint / Parameter/ Display Type]	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL – Snapshot							
Week 48 (ITT-E population)	Y[1]				Y[2]		Y
Study Outcomes				Y[1]			Y
Sensitivity Analyses							
Treatment Heterogeneity across randomization strata	Y						
Proportion of subjects without virologic or virologic/tolerability failure[3]	Y[6]	Y[4]					Y
Week 24 to Week 48 Bias Assessment[5]				Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Generated using the 'Intent-to-Treat Exposed' (primary), 'Per-Protocol' (sensitivity) and 'Intent-to-Treat' (sensitivity) populations.
2. Line plots, with 95% confidence intervals, for the proportion of subjects <50 c/mL by treatment group at each visit.
3. Outputs will be produced for Efficacy related discontinuation = Failure (ERDF) and Treatment related discontinuation = Failure (TRDF).
4. Kaplan-Meier Plot of Time to Failure – ERDF/TRDF
5. Required for the Week 48 reporting effort only.
6. By subgroup

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population

Snapshot Dataset

- The Snapshot algorithm treats all subjects 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, as well as subjects who switch their concomitant ART prior to the visit of interest in certain scenarios. Since changes in ART are not permitted in this protocol, all such subjects who change ART will be considered non-responders.
- Otherwise, virologic response or virologic non-response will be determined by the last available HIV-1 RNA assessment while the subject is On-treatment within the visit of interest analysis window (see Section 10.3).
- Full details of the Snapshot algorithm are in Appendix 9.

Model Specification

- The primary endpoint will be analysed using a stratified analysis with Cochran-Mantel-Haenszel (CMH) weights, adjusting for Baseline plasma HIV-1 RNA ($\leq$ vs. >100,000 c/mL) and CD4+ cell count ($\leq$200 cells/mm3 or >200 cells/mm3).
- The CMH estimate of the adjusted treatment difference will be calculated as a weighted average of strata-specific estimates of the treatment difference calculated within each of the following four Baseline analysis strata:
    - Plasma HIV-1 RNA $\leq$ 100,000 c/mL AND CD4+ $\leq$ 200 cells/mm3
    - Plasma HIV-1 RNA $\leq$ 100,000 c/mL AND CD4+ > 200cells/mm3
    - Plasma HIV-1 RNA > 100,000 c/mL AND CD4+ $\leq$ 200cells/mm3
    - Plasma HIV-1 RNA > 100,000 c/mL AND CD4+ > 200 cells/mm3
- If n_k is the number of DTG+3TC treated subjects, m_k is the number of DTG+TDF/FTC FDC treated subjects, and $N_k = n_k + m_k$ is the total number of subjects in the *k*th stratum, then the CMH estimate is given by

$$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

where,

$$W_k = \frac{n_k m_k}{N_k}$$

are CMH weights and d_k are estimates of the differences in response proportions between the two treatment arms, r_d-r_f, for the *k*th strata.

Primary Statistical Analyses

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

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

  using the variance estimator, var(d_{cmh}), given by [Sato, 1989], which is consistent in both sparse data and large strata. The full equation for this variance estimate is provided in Section 10.6.5.

- Non-inferiority will be concluded if the lower bound of the two-sided 95% confidence interval (CI) for the CMH adjusted difference in the proportion of patients who respond in the DTG +3TC group minus the proportion of patients who respond in the DTG + TDF/FTC FDC group is greater than -10%.

Model Results Presentation

- Adjusted CMH estimate of the difference in the proportion of responders between the two treatment groups (DTG + 3TC – DTG + TDF/FTC FDC) and corresponding 95% confidence interval.
- Figures: Line plots, with 95% confidence intervals, for the proportion of subjects below 50 c/mL by treatment group at each visit

Sensitivity and Supportive Statistical Analyses

1. Per-Protocol population analysis:
   - To assess the impact of significant protocol deviations, statistical analysis will be repeated using the Per-protocol population and compared for consistency with the results from the primary ITT-E population analysis. If both analyses show non-inferiority then the hypothesis that the antiviral effect of treatment with DTG+3TC is superior to treatment with DTG+TDF/FTC will be tested at the two-sided 5% level of significance. Superiority will be declared if the lower end of the 95% confidence interval in the ITT-E analysis is above 0%. If superiority is declared the p-value for superiority will also be calculated.
2. Intent-to-Treat population analysis:
   - Statistical analysis will be repeated using the Intent-to-Treat population and compared for consistency with the results from the ITT-E and PP populations.
   - In this analysis, subjects randomized but not exposed to study treatment will be classified as non-responders.
3. Treatment Heterogeneity across randomization strata:
   - The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately.
   - Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either, r_d-r_f are zero or one, and tests will be one-sided.
   - Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported for each level of the categorical variable. Tests of homogeneity will be assessed at the one-sided 10% level of significance.

Sensitivity and Supportive Statistical Analyses
4. Proportion of subjects without virologic (ERDF) or virologic/tolerability (TRDF) failure: • Estimated using the Kaplan-Meier nonparametric method based on the time to Confirmed Virologic Withdrawal (CVW) criteria met or treatment related/efficacy related discontinuation (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy). • The detailed algorithm for TRDF are listed in Section 10.13. The estimate of the standard error used to derive confidence intervals for the difference in proportions between treatment groups will be based on Greenwood's formula [Kalbfleisch, 1980] • The estimated proportion of subjects without Confirmed Virologic Withdrawal and not discontinued due to treatment related/efficacy related reasons at Week 48 will be presented by treatment group, along with estimated difference in proportions between treatment groups and its associated two-sided 95% CI. • Kaplan-Meier Plot of Time to Failure – Treatment/Efficacy related discontinuation = Failure 5. Bias sensitivity analysis • A sensitivity analysis will be performed at Week 48 to assess whether bias was introduced by the unblinded analysis performed at Week 24. • Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm will be compared between subjects who reached Week 48 results prior and after the Week 24 unblinding • No formal statistical hypothesis testing will be performed

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the Intent-To-Treat-Exposed population, unless otherwise specified. Week X represents each reporting effort (at Week 24/48/96/144).

Table 4 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 17: List of Data Displays.

Similarly to the plasma HIV-1 RNA <50 c/mL cut off, the following cut off will be derived and analysed:

- Plasma HIV-1 RNA<40 c/mL;

Table 4 Overview of Planned Efficacy Analyses

Endpoints	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL – Snapshot														
By Visit				Y										
By subgroup				Y[2]	Y[1]									
Study Outcomes by subgroup				Y										
Proportion of Subjects with Plasma HIV-1 RNA <40 copies/mL – Snapshot														
At Week X	Y													
Study Outcomes				Y										
By Visit				Y										
By subgroup	Y													
Plasma HIV-1 RNA over time – Observed[6]														
By Visit					Y[4]						Y[9]			
Subjects with Plasma HIV-1 RNA <50 c/mL by HIV-1 RNA and CD4+ Cell Counts subgroup														
Snapshot outcomes				Y										
Proportion of Subjects	Y[2]													
Kaplan - Meier														
Time to viral suppression	Y	Y[5]												
By Subgroup	Y	Y[5]												
Confirmed Virologic Withdrawal (CVW)														
By Visit				Y										
HIV-1 RNA distribution at time of suspected and confirmed Virologic withdrawal				Y			Y							
CD4+ Cell Counts														
At Week X								Y[3]	Y[7]					
By Visit				Y	Y[4]		Y				Y			Y
By subgroup								Y			Y			
Post-baseline HIV-1 Disease Progression[8]														
HIV Conditions including Recurrences				Y			Y							
HIV Conditions excluding Recurrences				Y										
HIV Disease Progressions				Y										

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.

- Individual = Represents FL related to any displays of individual subject observed raw data.
  1. Plot of 95% confidence intervals for unadjusted treatment difference in the proportion of subjects below 50 c/mL with overall and by subgroup.
  2. Repeat for Per Protocol population.
  3. Primary analysis method is multiple imputation MAR. Repeated for additional analyses using MMRM.
  4. Individual plasma HIV-1 RNA and CD4+ profiles for subjects with at least one SVW visit.
  5. Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups.
  6. Using observed case (OC) data which contains the data that is available at a particular time point, with no imputation for missing values.
  7. Line plots, with 95% confidence intervals for Adjusted Mean Change From Baseline in CD4+ Cell Count by treatment group at each visit.
  8. 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.
  9. Descriptive summary of the log10 change from baseline HIV-1 RNA by visit presented

8.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses
Endpoint(s)
• The time to viral suppression
Model Specification
• Nonparametric Kaplan-Meier method will be performed Overall and by Baseline HIV-1 RNA Subgroup. • Time of event will be the first viral load value <50 copies/mL • Subjects who withdraw for any reason without being suppressed will be censored at earliest of (day of study discontinuation, day of withdrawal visit, day of treatment discontinuation or study day 1050). • Subjects who have not been withdrawn and have not had viral suppression at time of the analysis will be censored at the earliest of (last viral load date or study day 1050). • Subjects who have completed the Double Blind and Open Label phases and have not had viral suppression will be censored at date of completion • CIs for Quartiles of time to viral suppression (including median) will be estimated using the Brookmeyer Crowley Method. • Cox proportional hazards model will be used to estimate the hazard ratio (DTG +3TC vs. DTG+TDF/FTC) and 95% confidence interval. • The generalised Wilcoxon procedure will be used to estimate a p-value for detecting a difference in cumulative incidence curves between treatment groups o Note: In general, the logrank test tends to be sensitive to distributional differences which are most evident late in time. In comparison, the generalised Wilcoxon test tends to be more powerful in detecting differences early in time (when the proportional hazard assumption are not met).
Model Results Presentation
• Number and percentage of subjects with event or censored at analysis week • Quartiles of time to viral suppression (including median) and 95% CI • Hazard ratio for viral suppression (DTG +3TC vs. DTG+TDF/FTC) and 95% CI • A p-value from Generalised Wilcoxon procedure • Figures: Kaplan-Meier Plots of Time to Viral Suppression

Secondary Statistical Analyses
Secondary Statistical Analyses
Statistical Analyses
Endpoints
• Change from baseline in CD4+ cell counts
Covariates & Factors
• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) • Note: Baseline CD4+ cell count will be used as continuous covariate as specified below.
Data Handling
• A multiple imputation technique will be used to deal with the missing data. (Multiple imputation (MAR) analyses are run at week 24 and 48 only.)
Model Specification
• Multiple imputation (MAR) analyses are run at week 24 and 48 only. • Using the OC dataset as a starting point, multiple imputations will be drawn from a multivariate normal imputation model (taking into account scheduled measurements prior to analysis Week X) with a Markov Chain Monte Carlo (MCMC) approach used to estimate posterior distributions. The MCMC method in the MI procedure in SAS will be used with multiple chains, 500 burn-in iterations, and a non-informative prior. A random seed number of 1349572 will be used in the SAS program. Where a subject has a monotone or non-monotone pattern of missingness, all of their missing observations can be imputed under this approach. The absolute value will be imputed before the change value is calculated. Imputations will be drawn separately for subsets of subjects according to their treatment group, i.e., based on means and variance-covariances from the same treatment group (Missing At Random (MAR) approach) conditioning on observed covariates (see above). • The imputations will be carried out 1,000 times. An ANCOVA, using the observed margins (OM) option, will be performed on each dataset produced adjusting for the covariates (listed above), treatment, and baseline value for the endpoint as a covariate, regardless of their significance. Rubin's imputation rules through PROC MIANALYZE in SAS will be used to combine the 1,000 estimated least squares means and difference to produce one estimated mean with 95% CI and associated p-value for the adjusted mean difference between each treatment group at Week X. • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted least squares means and corresponding standard errors (SEs) of adjusted least squares means will be presented for each treatment, together with estimated treatment difference (DTG+3TC – DTG+TDF/FTC FDC) and corresponding 95% confidence interval and p-value.
Additional Analyses
• Based on the OC dataset, the Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline CD4+ cell count value as a covariate, with visit as the repeated factor. • The model will make no further assumptions about the correlations between a subject's score (the correlation matrix for within-subject errors will be unstructured).

Secondary Statistical Analyses
• The repeated measures analysis will assume that the treatment difference can vary between visits (ie. a treatment*visit interaction will be included in the model), and separate estimates and 95% confidence intervals will be produced at each visit. The model will also assume that the effect of baseline score for the endpoint can vary between visits (ie. CD4+ cell count baseline score*visit interaction will be included in the model) • Line plots of LS means with 95% confidence intervals for Adjusted Mean Change From Baseline will be generated for each treatment group by visit
Subgroup Analyses
• Change from baseline in CD4+ cell count by each subgroup listed in Section 10.11. will be analyzed by an ANCOVA model, using the observed margins (OM) option, adjusting for the covariates (listed above), treatment, baseline value as a covariate, subgroup and treatment*subgroup interaction term regardless of their significance, using an OC dataset. • Results will be presented as adjusted point estimates, 95% confidence intervals.

Secondary Statistical Analyses
Endpoint(s)
• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm by subgroup
Subgroups
• See table in Section 10.11 for list of subgroups
Model Specification
• The proportion of subjects with plasma HIV-1 RNA <50 c/mL based on the Snapshot algorithm at analysis week will be summarized by treatment group and subgroup. • If the basic summary suggests an interaction, then a corresponding summary of study outcomes by subgroup will be produced. Note: These subgroup analyses will be exploratory and likely underpowered so that interpretation may therefore focus on point estimates as well as the lower bounds of 95% CIs for the treatment differences and response rates. Additionally, multiple comparisons are being made which inflates the risk of false positive findings. Therefore, if consistent findings across the multiple comparisons were observed then these analyses would still be suggestive of a generalizable finding of non-inferiority.
Model Results Presentation
• Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL and unadjusted difference in proportions between treatment groups and corresponding two-sided 95% CI will be presented by subgroup • Figures: Plot of 95% confidence intervals for the difference in proportion of subjects below 50 c/mL by subgroup.

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population, unless otherwise specified. Emergent AEs will be tabulated by treatment group and a total column. 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 summarising AE data, unless stated otherwise, the summaries will include post-baseline data.

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 17: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline					Max Post BL		
	Summary		Individual		Stats Analysis			Summary		Summary		
	T	F	F	L	T	F	L	T	F	T	F	L
Exposure												
Extent of Exposure	Y			Y [1,2]								
Adverse Events (AEs)												
All AEs by SOC and PT	Y			Y								
All AEs by Maximum Grade [3]	Y											
Drug-Related AEs by SOC and PT	Y			Y								
Drug-Related AEs by SOC and Maximum Grade [3]	Y											
AEs of Mexican Subjects				Y [4]								
Common AEs by Frequency [5]	Y	Y [6]										
Common Grade 2-5 AEs by Frequency [5]	Y	Y										
Common Drug-Related Adverse Events	Y	Y										
Various AE categories		Y										
Common Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y											
Common Drug-Related Grade 2-5 AEs [24]	Y											
Subject Numbers for Individual AEs				Y								
Relationship Between AE SOCs, PT and Verbatim Text				Y								
Post Baseline AE by Maximum Toxicity and Subgroups	Y											

Post-treatment AE by SOC and Maximum Toxicity	Y											
Serious and Other Significant AEs												
Fatal AEs	Y			Y								
Non-Fatal Serious AEs				Y								
Drug-Related Fatal AEs	Y			Y								
Serious AEs by SOC	Y											
Serious AEs for Mexicans				Y[4]								
Serious AEs for non-Mexicans				Y[4]								
Reasons for Considering as a Serious AE				Y								
Drug-Related Serious AEs by SOC	Y											
Drug-Related Non Fatal Serious AEs				Y								
Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y											
Drug-Related AE leading to withdrawal from study	Y											
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment and by Maximum Grade [3]	Y[18]			Y								
Individual Adverse Events				Y								
Possible Suicidality-Related Adverse Event (PSRAE)				Y[7]								
Cardiovascular events				Y								

Laboratory Values												
Clinical Chemistry				Y[8]				Y				
Lipids	Y							Y				
Fasted Lipid (Triglycerides, LDL, HDL and TC and TC/HDL) analysis	Y				Y[9,18]							
TC/HDL ratio										Y		
Hematology				Y [8]				Y				
Urine Dipstick				Y [8]								
Urine Concentration				Y [8]				Y				
Liver Chemistries											Y [10]	Y
NCEP shifts in lipids (LDL, HDL, TC, Triglycerides)										Y	Y[12]	
NCEP shifts in lipids (LDL, HDL, TC, Triglycerides) and TC/HDL ratio								Y[25]				
Biomarkers												
Bone biomarkers				Y	Y[18]	Y[19]		Y[18]				
Bone biomarkers (%)								Y				
Renal biomarkers				Y	Y[18]	Y[19]		Y[18]				
Renal biomarkers (%)								Y				
Inflammation Biomarkers				Y				Y				
Telomere length				Y				Y				
Emergent Laboratory Toxicities[13]												
Clinical Chemistry										Y		
Hematology										Y		
Fasting LDL Cholesterol Abnormalities of Grade 2 or Greater										Y[21]		
AST, ALT and Total Bilirubin Maximum Post-Baseline Emergent Toxicity By Baseline Hepatitis C Status										Y		

Other												
ECG [14]				Y								
Vital Signs at Screening				Y								
Liver Assessment	Y[23]			Y[15]								
Hepatobiliary Abnormality criteria – All post baseline and Treatment Emergent	Y			Y								
Columbia suicidality	Y			Y[16,20]								
Subjects who became Pregnant				Y								
Patient Profiles				Y[17]								
Characteristics of Post Baseline AESI[22]	Y											
Onset and Duration of the First Occurrence of Post Baseline AESI[22]	Y											
Total Duration of Post Baseline AESI[22]	Y											
Post Baseline Depression, Suicidal and Self-Injury Adverse Events by System Organ Class, Maximum Toxicity, and Prior History of Depression and Anxiety	Y											
PK				Y								
Weight	Y							Y				
BMI	Y							Y				

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Includes reason for any dose change/interruption.
2. Repeated for subjects at sites in Mexico at End of Study reporting only.
3. For AEs reported more than once by a subject, the most severe intensity will be included.
4. Only for End of Study reporting
5. Common AEs are those with >=2% incidence in either treatment group summarised by frequency.
6. Plots of incidence rates and relative risk with 95% CI for DTG + 3TC vs. DTG + TDF/FTC.
7. Four PSRAE listings: Event and Description (Section 1-Section 2), Possible Cause (Section 3), Section 4 and Section 5-Section8.
8. Listings for laboratory parameters with abnormalities for potential clinical concern, defined as any Grade1-4 toxicity.
9. Primary analysis method is multiple imputation MAR. Repeated for aditional analyses using MMRM. Lipids LOCF dataset will be used for all lipids summaries and analyses except for the analysis using multiple imputation methodology.
10. Scatter plot of baseline vs. maximum post-baseline for ALT. Scatter plot of maximum ALT vs. maximum Bilirubin.
11. Shift table summarising baseline vs. maximum post-baseline result
12. Bar chart for LDL, HDL, TC, Triglycerides and HDL/TC ratio.
13. Emergent Laboratory Toxicities - See protocol Appendix 6, Section 12.6).
14. Only collected at Screening or when a Cardiovascular event occurs.
15. Separate listings for Liver Event Results and Time of Event Relative to Treatment, RUCAM score, biopsy, imaging, past/ current conditions and FU.
16. Includes Baseline and lists all visits for a subject who reports any ideation or behaviour at any visit.
17. Patient profiles for subjects meeting protocol defined liver stopping criteria and for patients with CVW. Patient profiles can also be provided for any other subjects, as necessary for medical review.
18. Overall and by subgroup (listed in Section 10.11).
19. Line Plot of Adjusted Mean (95% CI) Change from Baseline
20. Separate outputs: Listing of False Positive Alerts with Corresponding Reasons and Listing of True Positives but not AES with Corresponding Reasons
21. Fisher's exact test Statistical analysis
22. AESI: Depression, Anxiety, Suicidality and Self injury, Drug Hypersensitivity, Rash, Insomnia, and Nightmare/abnormal dreams.
23. Summary of Liver Monitoring/Stopping Event Reporting
24. AEs those with >=1% incidence in either treatment group
25. Shit tables at Baseline to Week X

8.2.2. Planned Safety Statistical Analyses

Statistical Analyses
Endpoints
• Change from Baseline in Fasting Lipids (Triglycerides, LDL cholesterol, HDL cholesterol, Total Cholesterol and TC/HDL ratio)
Covariates & Factors
• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) • Baseline CD4+ cell count (≤ vs. >200 cells/mm^3) • Age
Data Handling
• Use the observed case dataset as a starting point. • If a subject has a non-fasting value, that visit will be set to missing.

Statistical Analyses
• If a subject initiates serum lipid-lowering therapy (as defined by ATC level 2='Lipid Modifying Agents') at Baseline, they will be excluded from the analysis. • If a subject initiates lipid-lowering therapy during the study, all visits after that date will be set to missing.
Model Specification
• If some Fasting Lipids will not be normally distributed then, the data will be log transformed and geometric means will replace arithmetic means, a 95% CI will replace the standard deviations and mean changes from baseline will be presented as geometric mean ratios. • A multiple imputation technique will be used to deal with the missing data (Multiple imputation (MAR) analyses are run at week 24 and 48 only). • Multiple imputations will be drawn from a multivariate normal imputation model (taking into account scheduled measurements prior to analysis Week X) with a Markov Chain Monte Carlo (MCMC) approach used to estimate posterior distributions. The MCMC method in the MI procedure in SAS will be used with multiple chains, 500 burn-in iterations, and a non-informative prior. A random seed number of 1349572 will be used in the SAS program. Where a subject has a monotone or non-monotone pattern of missingness, all of their missing observations can be imputed under this approach. The absolute value will be imputed before the change value is calculated. Imputations will be drawn separately for subsets of subjects according to their treatment group, i.e., based on means and variance-covariances from the same treatment group (Missing At Random (MAR) approach) conditioning on observed covariates (see above). • The imputations will be carried out 1,000 times. An ANCOVA, using the observed margins (OM) option, will be performed on each datasets produced adjusting for the covariates (listed above), treatment, and baseline value as a covariate, regardless of their significance. Rubin's imputation rules through PROC MIANALYZE in SAS will be used to combine the 1,000 estimated least squares means and difference to produce one estimated mean with 95% CI and associated p-value for the adjusted mean difference between each treatment group at Week X. • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted least squares means and corresponding standard errors (SEs) of adjusted least squares means will be presented for each treatment, together with estimated treatment difference (DTG+3TC – DTG+TDF/FTC FDC) and corresponding 95% confidence interval and p-value. • Note: For Fasting Lipids that are not normally distributed, the geometric mean and a 95% CI of geometric mean will be presented for each treatment, as well as geometric mean ratios and corresponding 95% CI and a p-value.
Additional Analyses
• With lipids LOCF dataset (Section 10.7.2.2), Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline fasting lipid value as a covariate, with visit as the repeated factor. • The model will make no further assumptions about the correlations between a subject's score (the correlation matrix for within-subject errors will be unstructured).

Statistical Analyses
• The repeated measures analysis will assume that the treatment difference can vary between visits (ie. a treatment*visit interaction will be included in the model), and separates estimates and 95% confidence intervals will be produced at each visit. The model will also assume that the effect of baseline score for the endpoint can vary between visits (ie. baseline score*visit interaction will be included in the model).
Subgroup Analyses
• Subgroup Analyses are run at week 24, 48 and 96 only. • Only Age (<50, vs ≥50) subgroup after week 48 will be analysed. • Change from baseline in fasting lipids by each subgroup listed in Section 10.11. will be analyzed by an ANCOVA model, using the observed margins (OM) option, adjusting for the covariates (listed above), treatment, baseline value as a covariate, subgroup and treatment*subgroup interaction term regardless of their significance, using an Lipid LOCF dataset. • Results will be presented as adjusted point estimates and 95% confidence intervals.

Endpoints
• The incidence of maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol
Data Handling
• The observed case (OC) dataset uses only the data that is available at a particular timepoint, with no imputation for subjects that have no post baseline values.
Model Specification/ Analysis Methodology
• Endpoints will be analysed for the comparison between DTG+3TC and DTG+TDF/FTC FDC by Fisher's exact test using the Safety Population
Model Results Presentation
• Incidence for each treatment group and a p-value for the difference in incidence between treatment groups.
Endpoints
• Change from baseline in bone biomarkers marker (bone specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D)
Covariates & Factors
• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) • Baseline CD4+ cell count (≤ vs. >200 cells/mm^3) • Age • Sex (Female vs. Male) • Race (White, African American/African Heritage, Asian, Other) • BMI (<vs. ≥ 25 kg/m^2) • Smoking status (Never vs. Former vs. Current Smoker) • Current Vitamin D use (Yes vs. No)
Data Handling
• A multiple imputation technique will be used to deal with the missing data (Multiple imputation (MAR) analyses are run at week 24 and 48 only).

Model Specification
• It is anticipated that at least some biomarkers will not be normally distributed and for those, the data will be log transformed and geometric means will replace arithmetic means, a 95% CI will replace the standard deviations and mean changes from baseline will be presented as geometric mean ratios. • Change from baseline will be analyzed for each bone biomarker for the comparison between DTG+3TC and DTG+TDF/FTC.
• Multiple imputation (MAR) analyses are run at week 24 and 48 only. • Using the OC dataset as a starting point, multiple imputations will be drawn from a multivariate normal imputation model (taking into account scheduled measurements prior to analysis Week X) with a Markov Chain Monte Carlo (MCMC) approach used to estimate posterior distributions. The MCMC method in the MI procedure in SAS will be used with multiple chains, 500 burn-in iterations, and a non-informative prior. A random seed number of 1349572 will be used in the SAS program Where a subject has a monotone or non-monotone pattern of missingness, all of their missing observations can be imputed under this approach. The absolute value will be imputed before the change value is calculated. Imputations will be drawn separately for subsets of subjects according to their treatment group, i.e., based on means and variance-covariances from the same treatment group (Missing At Random (MAR) approach) conditioning on observed covariates (see above). • The imputations will be carried out 1,000 times. An ANCOVA, using the observed margins (OM) option, will be performed on each datasets produced adjusting for the covariates (listed above), treatment, and baseline value as a covariate, regardless of their significance. Rubin's imputation rules through PROC MIANALYZE in SAS will be used to combine the 1,000 estimated least squares means and difference to produce one estimated mean with 95% CI and associated p-value for the adjusted mean difference between each treatment group at Week X. • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted least squares means and corresponding standard errors (SEs) of adjusted least squares means will be presented for each treatment, together with estimated treatment difference (DTG+3TC – DTG+TDF/FTC FDC) and corresponding 95% confidence interval and p-value. • Note: For biomarkers that are not normally distributed, the geometric mean and a 95% CI of geometric mean will be presented for each treatment, as well as geometric mean ratios and corresponding 95% CI and a p-value.
Additional Analyses
• Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and biomarker value at baseline as a covariate, with visit as the repeated factor. The OC dataset will be used for MMRM model. • The model will make no further assumptions about the correlations between a subject's score (the correlation matrix for within-subject errors will be unstructured). • The repeated measures analysis will assume that the treatment difference can vary between visits (ie. a treatment*visit interaction will be included in the model), and separates estimates and 95% confidence intervals will be produced at each visit. The model will also assume that

the effect of baseline score for the endpoint can vary between visits (i.e. baseline score*visit interaction will be included in the model). • Line plots of LS means with 95% confidence intervals for Adjusted Mean Change From Baseline will be generated for each treatment group by visit
Subgroup Analyses
• Subgroup Analyses are run at week 24, 48 and 96 only. • Change from baseline in bone biomarkers by each subgroup listed in Section 10.11. will be analyzed by an ANCOVA model, using the observed margins (OM) option, adjusting for the covariates (listed above), treatment, baseline value as a covariate, subgroup and treatment*subgroup interaction term regardless of their significance, using an OC dataset. • Results will be presented as adjusted point estimates and 95% confidence intervals.
Statistical Analyses
Endpoints
• Change from baseline in renal biomarkers (serum Cystatin C, urine albumin/creatinine ratio, urine protein/creatinine ratio, urine phosphate, eGFR (based on CKD-EPI-creatinine and CKD-EPI-cystatin C), serum creatinine, Urine Beta-2 Microglobulin/Urine Creatinine ratio and Urine Retinol Binding Protein/Urine Creatinine ratio).
Covariates & Factors
• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) • Baseline CD4+ cell count (≤ vs. >200 cells/mm^3) • Age • Sex (Female vs. Male) • Race (White, African American/African Heritage, Asian, Other) • Presence of diabetes mellitus (DM) (Yes vs. No) • Presence of hypertension (Yes vs. No)
Data Handling
• A multiple imputation technique will be used to deal with the missing data (Multiple imputation (MAR) analyses are run at week 24 and 48 only).
Model Specification
• It is anticipated that at least some biomarkers will not be normally distributed and for those, the data will be log transformed and geometric means will replace arithmetic means, a 95% CI will replace the standard deviations and mean changes from baseline will be presented as geometric mean ratios. • Change from baseline will be analyzed for each renal biomarker for the comparison between DTG+3TC and DTG+TDF/FTC. • Multiple imputation (MAR) analyses are run at week 24 and 48 only. • Using the OC dataset as a starting point, multiple imputations will be drawn from a multivariate normal imputation model (taking into account scheduled measurements prior to analysis Week X) with a Markov Chain Monte Carlo (MCMC) approach used to estimate posterior distributions. The MCMC method in the MI procedure in SAS will be used with multiple chains, 500 burn-in iterations, and a non-informative prior. A random seed number of 1349572 will be used in the SAS program. Where a subject has a monotone or non-monotone pattern of missingness, all of their missing observations can be imputed under this approach. The absolute value will be imputed before the change value is calculated. Imputations will be drawn separately for subsets of subjects according to their treatment

group, i.e., based on means and variance-covariances from the same treatment group (Missing At Random (MAR) approach) conditioning on observed covariates (see above).

- The imputations will be carried out 1,000 times. An ANCOVA, using the observed margins (OM) option, will be performed on each datasets produced adjusting for the covariates (listed above), treatment, and baseline value as a covariate, regardless of their significance. Rubin's imputation rules through PROC MIANALYZE in SAS will be used to combine the 1,000 estimated least squares means and difference to produce one estimated mean with 95% CI and associated p-value for the adjusted mean difference between each treatment group at Week X.
- Interactions between treatment and each of the covariates will not be assessed.

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Adjusted least squares means and corresponding standard errors (SEs) of adjusted least squares means will be presented for each treatment, together with estimated treatment difference (DTG+3TC – DTG+TDF/FTC FDC) and corresponding 95% confidence interval and p-value.
- Note: For biomarkers that are not normally distributed, the geometric mean and a 95% CI of geometric mean will be presented for each treatment, as well as geometric mean ratios and corresponding 95% CI and a p-value.

Additional Analyses

- Using OC dataset, the Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline biomarker value at baseline as a covariate, with visit as the repeated factor.
- The model will make no further assumptions about the correlations between a subject's score (the correlation matrix for within-subject errors will be unstructured).
- The repeated measures analysis will assume that the treatment difference can vary between visits (ie. a treatment*visit interaction will be included in the model), and separate estimates and 95% confidence intervals will be produced at each visit. The model will also assume that the effect of baseline score for the endpoint can vary between visits (ie. baseline score*visit interaction will be included in the model).
- Line plots of LS means with 95% confidence intervals for Adjusted Mean Change From Baseline will be generated for each treatment group by visit

Subgroup Analyses

- Subgroup Analyses are run at week 24, 48 and 96 only.
- Only baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL), baseline CD4+ cell count (≤ vs. >200 cells/mm3), Age (<50, vs ≥50) and presence of hypertension subgroups after week 48 will be analysed.
- Only Serum Cystatin C, eGFR (based on CKD-EPI-creatinine and CKD-EPI-cystatin C), Urine Beta-2 Microglobulin/Urine Creatinine ratio and Urine Retinol Binding Protein/Urine Creatinine ratio after week 48 will be analysed.
- Change from baseline in renal biomarkers by each subgroup listed in Section 10.11. will be analyzed by an ANCOVA model, using the observed margins (OM) option, adjusting for the covariates (listed above), treatment, baseline value as a covariate, subgroup and treatment*subgroup interaction term regardless of their significance, using an OC dataset.
- Results will be presented as adjusted point estimates and 95% confidence intervals.

8.3. Virology Analyses

8.3.1. Overview of planned Virology Analyses

The virology analyses will be based on the Viral Genotypic and Phenotypic population, unless otherwise specified.

Table 6 provides an overview of the planned analyses, with full details being presented in Appendix 17: List of Data Displays.

Table 6 Overview of Planned Virology Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Summary of Subject Accountability				
Genotypes Available	Y			
Phenotypes Available	Y			
Genotypic Resistance				
Genotypic results at Baseline and CVW[1]	Y[2]			Y[3]
Incidence of treatment-emergent genotype at time of CVW[1]	Y[2]			
Stanford Genotypic Susceptibility Score (S-GSS)				
Genotype at Baseline and Time of CVW by Genotypic Cut-Off	Y			Y
Phenotypic Resistance				
Incidence of treatment-emergent phenotype at time of CVW[1]	Y[4]			Y
Replication capacity				Y
Fold Change at Baseline and CVW	Y			
Net Assessment for Overall Susceptibility Score				
Overall Susceptibility Score (OSS)				Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Sample used for resistance testing is taken at the suspected visit date, and only tested once a subject confirms virological failure at a subsequent visit.
2. Separate outputs for INI and NRTI/NNRTI/PI mutations
3. All and Treatment Emergent
4. Separate outputs by phenotypic cut-off and by number of drugs to which subjects are resistant.

8.4. Health Outcomes Analyses

8.4.1. Overview of Planned Health Outcomes Analyses

The Health Outcomes analyses will be based on the Intent-To-Treat (Exposed) population, unless otherwise specified.

Table 7 provides an overview of the planned Health Outcomes analyses, with full details of data displays being presented in Appendix 17: List of Data Displays.

Table 7 Overview of Planned Health Outcomes Analyses

Endpoints	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Quality of Life														
EQ-5D-5L Utility Score/ EQ Visual Analogue scale (EQ VAS) - LOCF				Y			Y	Y	Y[1]		Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Line plot of Adjusted Mean (95% CI) Change From Baseline.

8.4.2. Planned Health Outcomes Statistical Analyses

Statistical Analyses
Endpoint(s)
• Change from baseline in EQ-5D-5L Utility Score • Change from baseline in EQ Visual Analogue Scale (VAS)
Covariates & Factors
• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) • Baseline CD4+ cell count (≤ vs. >200 cells/mm3)
Data Handling
• LOCF dataset will be used.
Model Specification
• If HO endpoints will not be normally distributed then, the data will be log transformed and geometric means will replace arithmetic means, a 95% CI will replace the standard deviations and mean changes from baseline will be presented as geometric mean ratios. • Any missing values should be imputed using LOCF. In the last observation carried forward (LOCF) dataset missing values will be carried forward from the previous, non-missing available On-treatment assessment from the same dimension. This technique will be applied for all missing values, regardless if the subject discontinued the treatment. Missing total values can then be calculated using a combination of present and carried forward individual items. • With LOCF dataset, Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline EQ-5D-5L value as a covariate, with visit as the repeated factor. • The repeated measures analysis will assume that the treatment difference can vary between visits (ie. a treatment*visit interaction will be included in the model),and separates estimates and 95% confidence intervals will be produced at each visit. The model will also assume that the effect of baseline score for the endpoint can vary between visits (ie. baseline score*visit interaction will be included in the model).

Statistical Analyses
• The model will make no further assumptions about the correlations between a subject's score (the correlation matrix for within-subject errors will be unstructured).
Model Results Presentation
• Adjusted means and corresponding standard errors (SEs) of adjusted means will be presented for each treatment by visit, together with estimated treatment difference (DTG+3TC – DTG+TDF/FTC FDC) and corresponding 95% confidence interval and p-value. • Figures showing the adjusted mean change from baseline with 95% CIs for each treatment group across visits in EQ-5D-5L Utility Score and EQ Visual Analogue scale.

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10. APPENDICES

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Section 10.2	Appendix 2: Time & Events
Section 10.3	Appendix 3: Assessment Windows
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10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

10.1.1. Exclusions from Per Protocol Population

Presented below are the criteria for subject exclusion from the Per Protocol population. Note: these are based on the ViiV-GSK 204861-205543 Study Deviation Rules Document v3.0-01Dec2017. Refer to the latest version of the rules document prior to finalisation of the per protocol population.

Subjects considered to have other significant protocol deviations, i.e., deviations which could affect the assessment of antiviral activity, could be flagged as excluded from the per-protocol population in the PD log based on clinical review of protocol deviations.

The following criteria define the protocol deviations which, if they occur prior or at an analysis timepoint of interest, will lead to exclusion of a subject from the Per-Protocol population for that analysis. Potential protocol deviations leading to exclusion from PP population will be reviewed by the study team to confirm that they meet these criteria. This review will occur before the clinical database has been frozen for analysis. Note: for significant protocol deviation 'Subject took/received incorrect IP, i.e., other than the one to which they were randomised for greater than 10% of the total time On-treatment' it will not be possible to identify whether subjects received a different treatment to the one they were randomised to until post unblinding.

Additional Statistical Programming Check:

In addition to the rules described below, subjects will also be excluded from the per protocol population for the following:

- Permanent discontinuation of IP/withdrawal due to a reason of "Protocol Deviation" (as recorded in the eCRF).

Ensure that the actual reason for the protocol deviation leading to permanent discontinuation is categorised under a rule specified in the rules document that results in exclusion from the per-protocol population.

The main categories are listed:

Significant Protocol Deviation Category	Deviation source
• Study treatment was unblinded prior to completion of the Week X visit	PPD
• Subject deviates from any inclusion or exclusion criteria, as recorded in the eCRF	PPD
• Subject took/received incorrect study treatment, for greater than 10% of the total time On-treatment; as evaluated at the time of the Week X analysis.	PAREXEL

Significant Protocol Deviation Category	Deviation source
• Interruption of study treatment for greater than 10% of the total time On-treatment, for reasons other than treatment-related adverse events/laboratory abnormalities, based on eCRF IP exposure; as evaluated at the time of the Week X analysis	PAREXEL
• Use of prohibited medication	PPD
• Subject's change (i.e. substitution or dose modification) of DTG, 3TC, TDF or FTC, but was not withdrawn from the study	PPD
• Subject became pregnant while on study	PPD

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Procedures	Screening Visit[a]	Double-blind Randomised Phase													Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																				
			4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Clinical and Other Assessments																							
Written informed consent	X																						
Inclusion/Exclusion criteria[e]	X	X																					
Demography	X																						
Prior ART history	X																						
Medical history[f]	X																						
Current medical conditions	X																						
Cardiovascular risk assessment, including vital signs[g]	X														X					X			
HIV risk factors and mode of transmission		X																					
CDC HIV-1 classification	X	X																					
HIV associated conditions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedures	Screening Visit[a]	Double-blind Randomised Phase														Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																					
			4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Columbia Suicidality Severity Rating Scale		X[h]	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam/Medical Decision Making[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG[j]	X																							
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[l]		X	X				X			X					X					X			X	
Laboratory Assessments																								
Plasma for HIV genotyping	X																							
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	
Lymphocyte subset	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	
Plasma for storage/inflammation biomarkers[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
Haematology	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
PT/INR	X																							

Procedures	Screening Visit[a]	Double-blind Randomised Phase														Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																					
			4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Fasting lipids and glucose[o]		X					X			X					X					X			X[p]	
Urinalysis and spot urine for protein analysis[q]		X					X			X					X					X			X	X
Pregnancy test[r]	S	U	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, anti-HBs, and HBV DNA[s]	X																								
HCV antibody	X																								
RPR	X																								
Renal and bone marker analytes (blood/urine)[t]		X					X			X					X					X			X	
Whole blood for virology/telomere length[u]		X[u]																			X[u]			X[u]	
Whole blood for telomere length[v]															X					X					
Study Treatment																									
IVRS/IWRS[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment		X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X			
Study treatment accountability (pill counts)			X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X		

anti-HBc = antibody to hepatitis B core antigen, anti-HBs = hepatitis B surface antibody, ART = antiretroviral therapy, CDC = Centers for Disease Control and Prevention, DNA = deoxyribonucleic acid, ECG = electrocardiograph, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, INR = international normalised ratio, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PT = prothrombin time, RNA = ribonucleic acid, RPR = rapid plasma reagin

a. Randomisation may occur as soon as all Screening results are available.
b. Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24, Week 48 and Week 96 must have HIV-1 levels re-assessed by a second measurement performed four weeks later at the Week 28, Week 52 visit and Week 100 visit, respectively. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL. Subjects with plasma HIV-1 RNA levels <50 c/mL at Week 24, Week 48 and Week 96 should not attend the Week 28 visit, Week 52 visit and Week 100 visit, respectively.
c. Subjects randomised to DTG plus 3TC who complete through Week 148 may enter the Continuation Phase. Subjects completing the Continuation Phase must return to the clinic for an End of Continuation Phase visit when transitioning to commercial supplies or to an alternate ART regimen if appropriate. At this visit, conduct study assessments as specified for all Continuation Phase visits with the exception of dispensing study treatment.
d. An in-clinic Follow-up visit will be conducted 4 weeks after the last dose of study medication for subjects with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the subject.
e. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1.
f. Full medical history will be conducted prior to randomisation and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
g. At screening, assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Body mass index (BMI) will be calculated within the eCRF. At Week 96 and Week 144, only weight will be measured.
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) is to be administered prior to randomisation.
i. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
j. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
k. Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. The questionnaire is recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct the questionnaire at Withdrawal if occurring prior to Week 144.
m. At Week 148, repeat HIV-1 RNA testing will only be performed for subjects with HIV-1 RNA ≥50 c/mL at Week 144.
n. Plasma samples for storage will be collected at each visit, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally, these samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable or as a priority need for genotypic and/or phenotypic analyses when subjects meet CVW criteria. Additionally, inflammation biomarkers (IL-6, hs-CRP) will be measured at Day 1, Week 48, Week 96 and Week 144 using stored plasma samples.
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
p. Only collect fasting lipids and glucose if the Withdrawal visit occurs at Week 24, Week 48, Week 96 or Week 144.
q. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.

r. Pregnancy testing will be conducted (females of reproductive potential only) on serum (S) samples with the exception of Day 1, which must be a urine (U) test to confirm status prior to administration of study treatment.
s. HBV DNA testing will be performed for subjects with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Subjects will have to return to the clinic to provide a sample for HBV DNA testing prior to randomisation.
t. Blood samples for renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2 Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D. Urine sample for renal biomarker assessments: RBP and Beta-2-Microglobulin. Only collect at the Withdrawal visit if it occurs at Week 24, Week 48, Week 96 or Week 144.
u. Whole blood samples may be used for virologic analyses as described in the protocol. A sample at Day 1 and a second sample at either Week 148 or at Withdrawal (if a subject is withdrawn prior to Week 148 will be taken for all subjects. Additionally, where possible, stored whole blood from Day 1 will be used for telomere length evaluation (while telomere length evaluation at Week 96 and Week 144 require a separate whole blood sample).
v. Whole blood samples for telomere length evaluation will be taken at Week 96 and Week 144 (where possible, the Day 1 evaluation will be done from the stored whole blood 'virology/telomere length' sample in footnote 'u')
w. At Screening, a subject number will be generated.

10.3. Appendix 3: Assessment Windows

Laboratory data, health outcomes (except for eCSSRS, which will use nominal visit labels as recorded on the eCRF) 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. The CVW algorithm will be derived using nominal CRF visit rather than using the assessment window defined below. 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.

10.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy/HO/lab	Snapshot endpoints/lipids, glucose, renal (serum creatinine, GFR BSA adj follow safety chem), bone, telomere, urinalysis, EQ5D & CSSRS	-28	≤-4	≤-4	Screen
		1	-3	1	Day 1
		29	2	42	Week 4
		57	43	70	Week 8
		85	71	98	Week 12
		113	99	126	Week 16
		169	127	210	Week 24
		253	211	294	Week 36
		337	295	378	Week 48
		421	379	462	Week 60
		7*w + 1	(7*w – 41)	(7*w + 42)	Week w w = 72, 84, 96,… 144
		Forcing snapshot window to be ±6 weeks, Week 148 nominal visit will be counted under Week 144 analysis window for HIV-1 RNA			
		1121	1051	1162	Week 160 (7*w-69d, 7*w+42d)
		1205	1163	1246	Week 172 (7*w-41, 7*W+42)
		Study Day of last dose + 28	> (Study Day of last dose + 1)	> (Study Day of last dose + 1)	Follow-up

NOTES :

- For key scheduled timepoints at Week 24/48/96/144, the windows have been defined to cover ± 6 weeks, regardless of the midpoint between adjacent target Study Days. The windows for the adjacent periods are adjusted accordingly.
- For parameters that are not scheduled to be assessed at particular visits, such as unscheduled visits or parameters measured at the wrong visit, the all-inclusive windows defined above will still be used; data summaries will be reported by scheduled visits. Assessments at unscheduled visits will be included in data summaries, and for 'any time On-treatment' time points and in data listings, as well any algorithms that make use of additional data (e.g. snapshot,).
- See Section 10.6.2 for how to handle multiple assessments within a time window.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy/ Safety/Virology	CD4+ cell count, safety lab (chem, hema) observed case for non-snapshot efficacy	-28	≤-4	≤-4	Screen
		1	-3	1	Day 1
		29	2	42	Week 4
		57	43	70	Week 8
		85	71	98	Week 12
		113	99	126	Week 16
		169	127	210	Week 24
		253	211	294	Week 36
		337	295	378	Week 48
		421	379	462	Week 60
		7*w + 1	(7*w – 41)	(7*w + 42)	Week w w = 72, 84, 96,…
		1009	967	1022	Week 144 (7*w-41d, 7*w+14d)
		1037	1023	1078	Week 148 (7*w-13d, 7*w+42d)
		1121	1079	1162	Week 160 (7*w-41, 7*w+42d)
		Study Day of last dose + 28	> (Study Day of last dose + 1)	> (Study Day of last dose + 1)	Follow-up

NOTES :

- For key scheduled timepoints at Week 24/48/96/144/148, the windows have been defined to allow analysis visits at week144 and week 148.
- For parameters that are not scheduled to be assessed at particular visits, such as unscheduled visits or parameters measured at the wrong visit, the all-inclusive windows defined above will still be used; data summaries will be reported by scheduled visits. Assessments at unscheduled visits will be included in data summaries, and for 'any time On-treatment' time points and in data listings, as well any algorithms that make use of additional data (e.g. snapshot,).
- See Section 10.6.2 for how to handle multiple assessments within a time window.

10.4. Appendix 4: Treatment States and Phases

10.4.1. Study Phases

All displays are for the Double Blind and Open Label phases combined, unless specified otherwise. All data collected up to the point of DBF will be included in summary statistics hence, for example, data collected beyond week 24 will be included in the week 24 reporting effort. In other words, all data collected up to the point of DBF will be included in summary statistics, which could be past week 24 for subjects enrolled early in the study. However, at the Week 144 analysis, summary statistics will include data up to Week 148 for both arms.

Data collected after Week 148 will be considered to be during the Continuation Phase of the study and will be not included in the table summaries for Week 144/148 reporting.

Treatment Phase	Definition*
Screening	Date < Day 1
Double Blind	Day 1 ≤ Date ≤ Week 96
Open Label	Week 96 < Date ≤ Week 148
Continuation Phase	Date > Week 148

*based on analysis windowing. For parameters without scheduled visit at week 148, data will be cut at Week 144 analysis visit, i.e. at upper analysis window bound, i.e. study day 1050.

All available data will be listed in listings with no cut-off for WK148 applied.

10.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

10.4.2.1. Treatment States for Laboratory, HIV Associated Conditions, Vital Signs, Health Outcomes and Genotypic and Phenotypic Data

Treatment State	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

10.4.2.2. Treatment States for AE Data

Treatment State	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. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date
Post-Treatment	If AE onset date is after the treatment stop date.

Treatment State	Definition
	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 If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on CRF.

NOTES:

- Partial AE start date will use imputation as described in Section 10.7
- 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 investigational product; in such a case the AE is assigned as Pre-treatment.
- If the IP Stop Date is missing, then any event with a start date on or after IP Start Date will be considered to be On-treatment.
  If the start date of the AE is after IP Stop Date but has been recorded as potentially related to IP, then it will be classified as On-treatment.

10.4.2.3. Treatment States for Prior/Concomitant/Post-Therapy Medications Data

- Prior medications are those taken (i.e., started) before the start date of investigational product.
- Concomitant medications are those taken (i.e., started or continued) at any time between the start date and stop date of IP, inclusive. Prior medications that were continued during this period are also considered as concomitant medications.
- Post-treatment medications are those started after the stop date of IP. Concomitant medications that were continued during this period are also considered as post-treatment medications.

It will be assumed that medication has been taken on the date in which it is reported as started or stopped. Also, for any medication starting on the same date as IP, it will be assumed that the medication was taken after the subject started taking IP.

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

- ART starting on study treatment stop date will be considered as only post-treatment and not concomitant. It is expected that after discontinuation of study treatment, a subject may immediately begin taking another ART. (Note: this is different to concomitant medications which are considered concomitant and post-treatment if they start on the IP stop date).

- ART stopping on study treatment start date will only be considered as prior and not concomitant. (Note: this is different to concomitant medications which are considered concomitant and post-treatment if they start on the IP stop date).

The table below is for concomitant medications only.

	Pre-treatment	On-treatment			Post-treatment		Prior	Conco-mitant	Post
		IP Start Date		IP Stop Date	IP Stop Date+1				
(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)			x————			————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

10.4.3. Post-treatment Assessments and Phases

On-treatment and Post-treatment assessments and events will be classified as occurring during the Double Blind, Open Label or the Continuation Phase of the study as follows:

- If a subject did not enter the Open Label Phase, then any Post-treatment data will be assigned to Double Blind Phase.
- If a subject did not enter the Continuation Phase, then any Post-treatment data will be assigned to the Open Label Phase.
- For subjects who did enter the Continuation Phase, any Post-treatment data will be assigned to the Continuation Phase.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
PPD Randomization System		Data Displays for Reporting	
Code	Description	Description	Order [1]
1	DTG + 3TC once daily	DTG + 3TC	1
2	DTG + TDF/FTC FDC once daily	DTG + TDF/FTC FDC	2

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints (unless stated otherwise) the baseline value will be the latest pre-dose assessment. This is generally expected to be from the Day 1 visit, although such values may be missing or unscheduled assessments may be performed before treatment start.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software and TSCG will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: \ARPROD\GSK3515864\mid204861\ : \ARPROD\GSK3515864\mid205543\
QC Spreadsheet	: \ARPROD\GSK3515864\ mid204861\<REPORTING_EFFORT>\documents : \ARPROD\GSK3515864\ mid205543\<REPORTING_EFFORT>\documents

Reporting Process
Analysis Datasets
• Analysis datasets will be created according to according to CDISC standards (SDTM IG Version 3.2 & AdaM IG Version 1.0. • For creation of AdaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented as SDTM.
Generation of RTF Files
• RTF files will be generated for each reporting effort.

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Actual time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • Reporting for Data Listings: • Actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). Relative time, relative to a reference date, is provided in listings where a date of an event or assessment is available. These reference dates will typically be the start date of treatment. • Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits
• Unscheduled visits will be assigned to a study visit using the all-inclusive windows defined in Section 10.3. • However, data summaries will only report visits that are planned assessment time points for each parameter (according to the T&E table). • Assessments at unscheduled visits will be included in data listings

Reporting Standards	
Invalid Laboratory Assessments	
• Certain laboratory endpoints are required to be collected in a fasting state, i.e., glucose and lipids (triglycerides, total cholesterol, HDL, LDL). If these endpoints are collected in a non-fasting state, then the results will be excluded from summaries; such results will be included in data listings with the fasting status noted.	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. Week 24/48/96/144 cut off date

10.6.1.1. To calculate the total time on treatment prior or at week 24

For the week 24 interim, it is necessary to define a cut-off for the calculation of total time on treatment during the Week 24 time period. This is for purpose of significant protocol deviation identification only for deviations that are being identified by PAREXEL.

The cut-off date is defined as follows:

- For subjects who have a Week 24 visit -> cut-off = Week 24 end date from Visit dataset (SV).
- For subjects who have withdrawn before Week 24 visit -> cut-off = the earliest of (Day of Study Discontinuation from DS, date of Withdrawal Visit from SV, Study day of permanent treatment discontinuation from EX).
- For subjects who have not withdrawn but no IP stop date or week24 visit date yet -> cut-off = IP start date + 210* - 1
  **upper bound of week24 window*

The last exposure data should use both Start Date of Treatment and End Date of Treatment in case the IP was interrupted and re-started.

This cut-off date applies for the calculation of total on treatment during Week

24, such as for denominator of dose interruption percentage.

A similar approach will be used for the Week 48/96/144 cut-off.

10.6.1.2. To check if the PD occurred prior or at week 24 viral load date (used for snapshot algorithm)

- For subjects who have Week 24 viral load date -> cut-off = Week 24 viral load date (used for snapshot algorithm) from LB dataset.
- For subjects who do not have a Week 24 viral load date:
  - if withdrawn before Week 24 Snapshot HIVRNA sample taken -> cut-off = the earliest of (Day of Study Discontinuation from DS, date of Withdrawal Visit from SV)
  - If missing data during week 24 window but on study-> cut-off = IP start date + 210* - 1
    **upper bound of week24 window*

A similar approach will be used for the Week 48/96/144 cut-off.

10.6.2. General

Multiple Measurements at One Time Point

- If there are multiple assessments within Screening window, the last assessment before Day 1 will be used
- If there are multiple assessments within Day 1 window, the latest pre dose assessment will be used
- If after window assignment (see Section 10.3), there are multiple valid assessments of a parameter within the same on-treatment 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 the mean of these values will be used. For HIV-1 RNA, the geometric mean of the number of copies will be used as opposed to the arithmetic mean
- 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 or LOCF).
- In the event of laboratory re-tests being performed the last re-test in the visit window will be used. For example:
- *If a subject had a week 24 viral load and then two re-tests (ie three viral loads labeled as week 24, unscheduled 1 unscheduled 2). and the first two viral loads were within the upper bound of the week 24 visit (Day 210) but the last re-test was slotted to week 36 then the last re-test would not be used for the week 24 snapshot.*
- *If a subject had a week 24 viral load but the re-test was performed on Day 220 (week 36) then the re-test viral load would not be used for the week 24 snapshot.*

Study Day

- Calculated as the number of days from treatment start date:
    - Ref Date = Missing → Study Day = Missing
    - Ref Date < Treatment start Date → Study Day = Ref Date – treatment start Date
    - Ref Date ≥ Treatment start Date → Study Day = Ref Date – (Treatment start Date) + 1

Note that Treatment Start Date is considered to be on Study Day 1 and the day before this is Study Day -1; i.e., there is no Study Day 0.

Post-baseline

- Post-baseline refers to the combined time periods of On-treatment and Post-treatment.
- Post-baseline may be further specified according to phase of the study: Double-Blind, Open-Label and Continuation.

Emergent

- Emergent refers to AE Severity/ Lab toxicity that develops or increases in intensity after baseline

Study Drug

- Study Drug refers to either Investigation Product DTG + 3TC or DTG + TDF/FTC FDC.

10.6.3. Study Population

Demographics

Age

- Age, in whole years, will be calculated with respect to the subject's Screening visit where year of birth is collected.
- For the purpose of calculating age the '30th June' is imputed as the date and month of birth for all subjects.
- Birth date 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 subject will not be calculated and will remain missing.

Framingham Risk Equation

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

for females:

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

for males:

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

where

$$S0(t) = \begin{cases} 0.95012, \text{females} \\ 0.88936, \text{males} \end{cases}$$

TC = total serum cholesterol (mg/dL),
HDL = serum HDL cholesterol (mg/dL),
SBPu = systolic blood pressure (mmHg) if subject is not treated for high blood pressure (note that if a subject is treated for high blood pressure then log(*SBPu*) = 0)
SBPt = systolic blood pressure (mmHg) if subject is treated for high blood pressure (note that if a subject is not treated for high blood pressure then log(*SBPt*) = 0)

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

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

Demographics
• A subject will be considered as treated for high blood pressure if during screening it has specified that is suffering from hypertension. • A subject is classified as diabetic if current or past is indicated in the medical conditions eCRF for Type 1 or Type 2 diabetes mellitus, or diabetes mellitus. • Smoking status is collected in the eCRF on Day 1. A current smoker is defined as currently smoking/using tobacco or has smoked/used tobacco within the previous 6 months; a former smoker is defined as previously smoked/used tobacco products and has not smoked/used tobacco products within the previous 6 months. • This calculation will not be performed for subjects who have indicated current or past myocardial infarction conditions on the eCRF. These subjects will not be included in summary statistics of risk, but will be counted in the highest category of risk in the summary by category.

10.6.4. Safety

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • If DTG and blinded background are not started on the same day, the earliest start date and latest stop date of the two will be used. • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • Missing Treatment Stop Date will be imputed, for purposes of calculating exposure, as the date of last visit or the recorded date of withdrawal/completion, whichever is earlier. • Actual exposure will be calculated where the duration of any dosing interruptions based on eCRF data will be subtracted from the result above. • The ratio (percentage) of duration of interruptions to the overall exposure (i.e. study treatment stop date – study treatment start date+1) will be used to define protocol deviation leading to exclusion from PP Population due to study treatment interruption (i.e. >10%). Refer to Section 10.6.1 for details.
Adverse Events
AE Severity – DAIDS Grading
• The DAIDS grading (VERSION 2.0, November 2014) for severity of clinical adverse events will be performed. • See protocol for DAIDS grading criteria.
Adverse Events of Special Interest (AESI)
The preferred terms for each AESI will be updated on an ongoing effort before each formal analysis in a separate document. The following table below shows the AESI categories

AESI
Anxiety

Extent of Exposure

Depression
Drug Hypersensitivity
Insomnia
Nightmare/Abnormal Dreams
Rash
Suicidality and self-injury

Laboratory Parameters

- 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 significant digits 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 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< 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
Fasted glucose	Hypoglycaemia	Hyperglycaemia
Sodium	Hyponatremia	Hypernatremia
Potassium	Hypokalemia	Hyperkalemia
Calcium	Hypocalcaemia	Hypercalcaemia

National Cholesterol Education Program (NCEP) Lipid 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

Laboratory Parameters

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

Glomerular Filtration Rate (GFR)

- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Levey et al. 2009] will be used by the central laboratory to provide an estimate of GFR, in mL/min per 1.73 m2, as follows:

$$\text{GFR} = 141 \times \min\left(\frac{\text{CRT}_{\text{mg/dL}}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\text{CRT}_{\text{mg/dL}}}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{Age}} \times [1.018 \text{ if Female}] \times [1.159 \text{ if Black}]$$

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.

Total Cholesterol / HDL Cholesterol Ratio

- When both total cholesterol and HDL cholesterol results are available from the same date for a subject, 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

Hepatitis Status

- Hepatitis C status will be determined using antibody (IgM or IgG) and/or hepatitis C virus (HCV) RNA assessments performed during screening or during the conduct of the study.
- 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
- Antibody (IgM or IgG) status with 'BORDERLINE' or 'REACTIVE' will be considered Positive
- A subject will be considered positive for hepatitis B virus (HBV) if they have a positive surface antigen or detectable HBV DNA result during screening. Subjects positive for HBV are not allowed to enter the study.

Other Safety Endpoints
Columbia Suicide Severity Rating Scale (C-SSRS)
• Missing data will not have any imputation performed. • A positive alert is triggered if a subject has reported suicidal ideation/behaviour in categories 4-9. • Questions in categories 3-5 will be triggered if suicidal ideation is reported in categories 1 or/and 2.

• Incomplete calls:
  ○ when no complete call is databased on the same day, the data from the incomplete call will be used
  ○ if a subject has only an incomplete call, and it resulted in a positive alert, the relevant pages in the CRF should be completed, even though the call was incomplete
  ○ when a complete call is databased on the same day, the data from the complete call will be used in the summaries.
• Duplicate calls, if they occur on the same day:
  ○ Both calls will be reported in the listings.
  ○ For summary tables, the entry with latest time record will be used.
  ▪ The exception to this is where an investigator's assessment of true positive alert (recorded in the eCRF) relates only to an earlier duplicate call. In such situations the earlier 'positive' alert will be selected over the later 'negative' assessment thus ensuring both the positive alert and the resulting true positive assessment by the investigator are selected for summary.
• Relevant CRF pages will be completed based on the latest entry (if it was a positive alert).
• Baseline evaluation includes 'Lifetime' and 'Current History' data on ideation and/or behaviour. Subjects with timing of assessment not done per protocol are noted and their Lifetime' and 'Current History' data are included in the baseline summary despite being performed at post baseline.
• Post-baseline evaluation includes 'Since Last Assessment' data on ideation and/or behaviour. Subjects with timing of assessment done not per protocol are noted and their 'Since Last Assessment' data are included in the post-baseline summary despite their assessments being performed on Study Day 1.
• Positive Alerts with a status of 'Not Applicable' contribute to counts of positive alerts but not to counts of either true or false positive alerts.
• A true positive alert is defined as an eCSSRS positive alert (any question 4 to 9 with a response of 'yes') where the eCSSRS positive alert is consistent with clinical judgement.
• Subjects may have more than one type of suicidal ideation or behaviour.

10.6.5. Efficacy

HIV-1 RNA

Snapshot

- The Snapshot algorithm is intended to be primarily a virologic assessment of the endpoint, and as such follows a "virology first" hierarchy.
- Virologic Success (e.g., <50 c/mL) or Virologic Failure within an analysis window (see Section 10.9) is typically determined by the last available HIV-1 RNA measurement in that window while the subject is On-treatment.
- When no HIV-1 RNA data is available within a window, a subject cannot be a Virologic Success. Depending on the reason for lack of data, the subject will be classified as a Virologic Failure 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 subject 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 subject withdraw for reasons other than AE and was not suppressed at the time, they will be a Virologic Failure.
- For each scheduled assessment time, the Snapshot response rate for a given threshold (e.g., <50 c/mL) is defined as:

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

- Full details of the algorithm, including the handling of special cases, are included in Section 10.9.

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 <40 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., 39 or 10,000,000 c/mL, respectively, for the given examples. Data listings will show the censored values as provided.

HIV-1 RNA

Target Detected / Target Non Detected

- When a measurement of plasma HIV-1 RNA is below the limit of quantification (i.e. 40 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 <40 c/mL characterised as "Target Non Detected" or "Target Detected" will be captured in the database.

Variance Estimator of Cochran Mantel-Haenszel Risk Difference

$$\hat{\text{var}}\left(\hat{d}_{cmh}\right)=\frac{\hat{d}_{cmh}\left(\sum P_k\right)+\sum Q_k}{\left(\sum n_k m_k / N_k\right)^2}=\frac{\hat{d}_{cmh}\left(\sum P_k\right)+\sum Q_k}{\left(\sum W_k\right)^2}$$

where

$$P_k=\frac{n_k^2 y_k - m_k^2 x_k + n_k m_k (m_k - n_k)/2}{N_k^2}$$

$$Q_k=\frac{x_k (m_k - y_k)/N_k + y_k (n_k - x_k)/N_k}{2}$$

CVW Derivation

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 5.4.1.2) will not be used when programmatically identifying CVW.
- A patient can only be classified as CVW for the analyses if the patient has not withdrawn IP at the time of the HIV-RNA value. Note: study drug interruptions will not be taken into account when programmatically identifying CVW.
- Additional guidelines specified in the protocol related to patient management only and will not be taken into account when programmatically identifying CVW.

There are 3 parts to the derivation of CVW.

Virologic Non-response (Parts 1 &2)

- A decrease in plasma HIV-1 RNA of less than 1 log10 c/mL at Week 12 or Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24.

Virologic Rebound (Part 3)

- Confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL at any time (not necessarily immediately) after prior confirmed suppression to <200 c/mL.

HIV-1 RNA

If the calculation results in both rebound and non-response, it would be reported as a rebound.

Part 1. A decrease in Plasma HIV-1 RNA of less than 1 log10 c/mL only at week 12 or Week 16, with subsequent confirmation, unless Plasma HIV-1 RNA is <200 c/mL

- This applies to Week 12 and Week 16 data only (programming note: include unscheduled visits as a part of a confirmation)
- If there is a decrease < 1 log10 from Baseline at Week 12 or Week 16 and HIV-1 RNA >=200 c/mL, then -> suspected virologic withdrawal
- If there is a confirmatory sample, then check if there is a decrease <1 log10 from Baseline and the HIV-1 RNA >=200 c/mL then -> confirmed virologic withdrawal
- Example: Part 1, subject PPD – confirmed virologic withdrawal on 18-Jun-15

Part 2: Confirmed Plasma HIV-1 RNA levels >=200 c/mL on or after Week 24

- If patient is not already a confirmed VF due to the rules in Part 1, we can then continue to check the results from Week 24 onwards
- If a patient has a sample on/after Week 24 and the result is >=200 c/mL then -> suspected virologic withdrawal.
- If a patient, then has a 2nd consecutive sample >=200 c/mL then -> confirmed virologic withdrawal.
- Example: Part 2, subject 1064 - confirmed virologic withdrawal on 06-Oct-15

Part 3: Confirmed rebound in plasma HIV-1 RNA levels to >=200 c/mL after prior confirmed suppression to <200 c/mL

- Patient must have 2 consecutive values <200 c/mL, followed at any time (not necessarily immediately) by 2 consecutive values >=200 c/mL.
- Once a patient has 2 consecutive values <200 c/mL, if any following value is >=200 c/mL then -> suspected rebound
- If a patient, then has a 2nd consecutive sample >=200 c/mL then then -> confirmed rebound
- Example: Part 3, subject PPD – confirmed rebound on 26-Aug-15

Example: Part 1, subject PPD

subject	visit	visit date	c/mL	log10 c/mL	log10 decrease from BL	CV outcome	comments
PPD	Baseline	16-Feb-15	3398	3.53			
	Week 4	PPD	39	1.59	1.94		
	Week 8		2354	3.37	0.16		
	Week 12		368742	5.56	-2.03	Suspected virologic withdrawal	<1 log 10 decrease from baseline,

HIV-1 RNA

							and value >200 c/mL
PPD	Week 12 retest	PPD	17293	4.24	-0.71	Confirmed virologic withdrawal	<1 log 10 decrease from baseline, and value >200 c/mL

Example: Part 2, subject PPD

subject	visit	visit date	c/mL	log10 c/mL	log10 decrease from BL	CV outcome	comments
PPD	Baseline	28-Mar-15	38286	4.58			
	Week 4	PPD	332	2.52	2.06		
	Week 8		400	2.60	1.98		
	Week 12		<50	<1.70	2.99		
	Week 24		87394	4.94	-0.36	Suspected virologic withdrawal	value >200 on/after week 24
	Week 24 retest		213	2.62	1.97	Confirmed virologic withdrawal	Consecutive value >200 on/after week 24

Example: Part 3, subject PPD

subject	visit	visit date	c/mL	log10 c/mL	log10 decrease from BL	CV outcome	comments
PPD	Baseline	02-Apr-15	303007	5.48			
	Week 4	PPD	170	2.23	3.25		
	Week 8		140	2.15	3.33		
	Week 12		166	2.22	3.26		
	Week 16		29153	4.46	1.02	Suspected rebound	2 consecutive values <200,

HIV-1 RNA							
							followed by an initial value >=200
PPD	week 16 retest	PPD	454	2.66	2.82	Confirmed rebound	2nd consecutive sample >=200
	Withdrawal	17-Sep-15	<40	1.59	3.89		

10.6.6. Viral Genotyping and Phenotyping

Genotype

General considerations

- Nominal and analysis window will be included in the listings.
- For summary purposes analysis window will be used.
- Note: Resistance testing will be performed on samples collected at the SVW timepoint (i.e. the timepoint of the initial HIV-1 RNA result which meets one of the Virologic Withdrawal criteria and will be subsequently confirmed in a repeat HIV-1 RNA test. The SVW timepoint is noted as the CVW timepoint in listings and summaries.

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.
- Treatment emergent mutations: need to meet below three criteria:
  1. New mutation: observed during treatment comparing to baseline at the same codon with the class/region.
  2. Mutations are based on prespecified lists usually identified in the RAP.
     a. Integrase: may use a list generated by Virology that may include non-IAS guidance mutations derived using the Stanford database (e.g., mutations with penalty score >=15; https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/), or other reliable sources. Note the list may change over time. Usually the major mutations are the ones with evidence of strong resistance to the ART drug.
     b. All other classes: defined by the International Antiviral Society-USA (IAS-USA).
  3. ART Drug class related: based on the class of the ART the subjects are taking during the treatment and the new major mutation within that class will be considered.

Genotype

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'

Prespecified Lists – Resistance Associated Mutations

1. Known INI (INSTI) mutations associated with the development of resistance to RAL, EVG or DTG:

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A/I/K**, L74M, **E92Q/V**/G, Q95K, T97A, G118R, F121Y, E138A/K, G140A/C/S, **Y143C/H/R/K/S/G/A, P145S**, **Q146P**, **S147G**, **Q148N/H/K/R**, **V151**I/**L**/A, S153F/Y, **N155H/**S/T, E157Q, G163R/K, S230R, R263K, L68V/I*, L74I*, E138T*, V151I*, G193E*

INI (INSTI) Prespecified List
NOTES:

- Current listing may be modified in case of additional substantive data availability.
- Most INI mutations listed taken from Stanford HIV Resistance Database (http://hivdb.stanford.edu/DR/cgi-bin/rules_scores_hivdb.cgi?class=INI cited 28 Feb 2014) and accessed on Oct 27th 2016.
- Most INI mutation listed had a score of ≥15; and INI substitutions listed above in bold had a score of =60.

*Mutations denotes additional INI mutations added as they were identified during in vitro passage of DTG or seen in a previous DTG study in INI-experienced subjects (ING112574).

2. 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. Note that NRTIs A62V, V75I, F77L, and F116Y all need to be present together with Q151M to be resistant, so are not major mutations alone.

Class	Mutations
NRTIs	M41L, K65R/E/N, D67N, 69 insert, K70E/R, L74V, Y115F, M184V/I, L210W, T215Y/F, K219Q/E; [A62V, V75I, F77L, F116Y, Q151M]
NNRTIs	L100I, K101E/P, K103N/S, V106A/M, V108I, E138/A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C, M230I/L,
PIs	D30N,V32I , M46I/L, I47A/V, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S, L90M

3. Note: 2017 Drug Resistance Mutations Update Volume 24, Issue 4, December 2016/January 2017

Susceptibility Scores

Stanford Genotypic Susceptibility Score (GSS)

Genotype

- 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 HIVdb system, each HIV-1 drug resistance mutation is assigned a drug penalty score. The penalty scores for each drug resistance mutation are available at
  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/. Scores for particular patterns of INSTIs are also available at 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. 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 subject defined as the sum of the resistance scores for each of their background drugs.

Phenotype

Monogram Genotypic Susceptibility Score (GSS)

- Monogram GSS score will be reported in a listing, but will not be used for summary tables.
- Genotypic sensitivity to each drug will be assigned using the Monogram resistance score for each background drug provided in the database.

Score	Sensitivity
1	Sensitive
0	Resistant

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).

Genotype

- 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 subject's ART and categorised as 0, 1, 2, or 3. OSS values will be calculated only for the time of CVW when net assessment is available.

Decision tree 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. 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.
- For examples please refer to decision tree below.

Background:

- PSGT - provides both geno and pheno data for PRO/RT (NRTI and NNRTI) only
- PSIN - Provides pheno data on Integrase only
- GSIN - Provides geno data on Integrase only
- PSGT+IN - Secondary assay used if PSGT or GSIN assay fails; it provides both geno and pheno data on PRO, RT and Integrase

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 CVW samples, then PSGT+IN assay will not be performed, no PSGT+IN data should be generated.

Assays	Baseline	CVW
PSGT	**y**	**y**
PSIN	**y**	**y**
GSIN	**y**	**y**

Genotype

Scenario 2: 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 CVW sample but PSIN and GSIN fail to work, in this scenario, use data generated from PSGT+IN assay on both Baseline and CVW sample for analyses, regardless of obtained PSGT assay data.

Assays	Baseline	CVW
PSGT	y	y
PSIN	n	n
GSIN	n	n
2nd PSGT+IN	**Y**	**Y**

Scenario 3: If PSGT, PSIN and GSIN all work for baseline samples; PSGT works for CVW but PSIN and GSIN fail, while PSGT+IN on CVW sample works, then use CVW PSGT+IN (PR, RT and INSTI) to do comparison with PSGT, PSIN and GSIN baseline data (do not use PSGT at CVW data vs. PSGT at Baseline)

Assays	Baseline	CVW
PSGT	**y**	y
PSIN	**y**	n
GSIN	**y**	n
2nd PSGT+IN	-	**Y**

Scenario 4: If PSGT works but GSIN and PSIN both fail on baseline sample, then 2nd PSGT+IN assay might be performed. And if PSGT, PSIN and GSIN all work for CVW sample, then use Baseline PSGT+IN data to do comparison with CVW Primary assay data, regardless of PSGT Baseline data. In other words, don't use PSGT Baseline to do comparison of PSGT part of PSGT+IN assay data for CVW sample

Assays	Baseline	CVW
PSGT	y	**y**
PSIN	n	**y**
GSIN	n	**y**
2nd PSGT+IN	**Y**	-

10.6.7. Health Outcomes

European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)
• The EQ-5D is a quality of life instrument that provides a EQ-5D-5L Utility Score and the EQ Visual Analogue scale (EQ VAS)
EQ-5D-5L
• The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with five levels for each dimension from level 1 = no problem to level 5 = extreme problems. • The number of possible health states is 5^5 = 3125. • The health state is defined by combining the levels of answers from each of the 5 questions. • Each health state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. • The health state 5 digit code is translated into the utility score, which is valued up to one (representing perfect health) with lower values meaning worse state, according to the methodology described in Devlin,.2016, Section 3.4. The UK values set described in, Section 3.4 will be used for all subjects regardless of their country origin. • The numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. • Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values. • Observed values will be used in listing.
EQ visual Analogue scale (EQ VAS) 'Thermometer'
• Self-rated current health status • Ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail

General	• Subjects are considered to have completed the study if they satisfy one of the following:
	  ○ Randomly assigned to either treatment arm, completed the Open-label Randomised Phase including the Week 148 visit, and did not enter the Continuation Phase;
	  ○ Randomly assigned to DTG plus 3TC, completed the Open-label Randomised Phase including the Week 148 visit, entered and completed the Continuation Phase (defined as remaining on study until DTG and 3TC are both locally approved for use as part of a dual regimen and the single entities of DTG and 3TC are available to patients (e.g. through public health services) or the DTG/3TC FDC tablet, if required by local regulations, is available or development of the DTG plus 3TC dual regimen is terminated).
	• Withdrawn subjects will not be replaced in the study.
	• All available data from subjects who were withdrawn from the study will be listed.

10.7.2. Handling of Missing Data

10.7.2.1. Handling of Partial and Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Exposure	• If study treatment stop date is 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. • Partially Missing Stop Day: Last day of the month or last month of the year will be used, unless this is after the stop date of study treatment or withdrawal date; in this case the earliest of the two dates will be used.

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing.
	• If the full date cannot be ascertained, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  ○ Completely missing dates: (i.e. no year specified) will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
	  ○ Partially Missing Start Day: First day of the month or first month of the year will be used unless this is before the start date of study treatment; in

Element	Reporting Detail
	this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4:Treatment States and Phases. ○ Partially Missing Stop Day: Last day of the month or last month of the year will be used, unless this is after the stop date of study treatment or withdrawal date; in this case the earliest of the two dates will be used. • The recorded partial date will be displayed in listings
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, the first day of the month will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, last day of the month will be used for the day and 'Dec' will be used for the month. ○ For medications recorded in the eCRF as prior ART, the earlier of this imputed date or the day before IP start will be used. • The recorded partial date will be displayed in listings.

10.7.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Snapshot	• In the Snapshot dataset, subjects without HIV-1 RNA data in the assessment window for the visit of interest (due to missing data or discontinuation of IP prior to the visit window) are classified as non-responders in the derivation of the proportion of subjects with HIV-1 RNA < 50 c/mL. The nature of this missing data will be further classified in Snapshot summaries as either 'Virologic Failure' or 'No Virologic Data at Week X'; see Section 10.9 for full details
Lipids LOCF	• If subjects initiate lipid-lowering agents Post-baseline, then the last available fasted On-treatment lipid values prior to the initiation will be used in place of future, observed On-treatment values. • Imputation will continue even if the subject discontinues the lipid-lowering agent. • If the missing data was due to other reasons, no data will be imputed. • Subjects on lipid-lowering agents at baseline will be excluded from this dataset. • This dataset will be used for all summaries of lipids data.

Element	Reporting Detail
LOCF	• This dataset will be used for all summaries of health outcomes data. • In the last observation carried forward (LOCF) dataset missing values will be carried forward from the previous, non-missing available On-treatment assessment from the same dimension. • This technique will be applied for all missing values, regardless if the subject discontinued the treatment.
Observed Case (OC)	• This dataset uses only the data that is available at a particular timepoint, with no imputation for missing values.

10.8. Appendix 8: Values of Potential Clinical Importance

Element	Reporting Detail
Laboratory Values and Adverse Events	• The DAIDS grading for severity of laboratory toxicities and clinical adverse events is included in the protocol. • The central laboratory will flag lab parameter toxicities directly in the provided datasets.

10.9. Appendix 9: Snapshot

10.9.1. Snapshot Algorithm Detailed Steps

Please note that no change in the background ART is permitted for this protocol.

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 ('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 ART
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 ART
3: If ***non-permitted*** change in background therapy ***during*** Week 48		
• Last on-treatment VL during Week 48 prior to/on the date of change ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window and HIV-1 RNA >= 50 copies/mL
• Last on-treatment VL during Week 48 prior to/on the date of change <50 c/mL	HIV1-RNA < 50	
• No VL during Week 48 prior to/on the date of change	HIV1-RNA ≥ 50	Change in ART
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 ART
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 and HIV-1 RNA

Condition ('Week 48' indicates Week 48 window)	**Response**	**Reasons**
		>= 50 copies/mL
5: If none of the above conditions met		
5.1 VL available during Week 48		
• Last on-treatment VL during Week 48 ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window and HIV-1 RNA >= 50 copies/mL
• Last on-treatment VL during Week 48 <50 c/mL	HIV1-RNA < 50	
5.2 No VL during Week 48		
5.2.1 if subjects still on study (i.e. IP has not been permanently stopped up to Week 48)	No virologic data at Week 48 Window	On study but missing data in window
5.2.2 If subjects 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 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 Conclusion Form)		
• 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
• Last on-treatment VL ≥ 50 c/mL AND withdrawal due to Lack of efficacy	HIV1-RNA ≥ 50	Disc. for lack of efficacy
• Last on-treatment VL ≥ 50 c/mL AND withdrawal due to all other non-safety related reasons	HIV1-RNA ≥ 50	Dis. for other reason and HIV-1 RNA >= 50 copies/mL

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

10.10. Appendix 10: Multicenter Studies

10.10.1. Methods for Handling Centres

Data will be summarised for all centres combined. Country will be treated as an exploratory subgroup for analyses of the secondary efficacy endpoint as described in Section 8.1.

10.11. Appendix 11: Examination of Covariates, Subgroups & Other Strata

10.11.1. Handling of Covariates, Subgroups & Other Strata

- The following is a table of covariates that may be used in descriptive summaries, statistical analyses and analyses by subgroup.
- Model terms that are categorical in nature or expressed as categorical terms will be included as 'factors' (e.g., 'Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL)'); otherwise model terms will be included as continuous scale 'covariates' (e.g., 'Age').
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial, i.e. the race subgroup (African American/African Heritage; Non-African American/African;) might be used if percentage of subjects is small within a particular subgroup in other race categories.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Randomization Strata using Baseline Values	• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL); • Baseline CD4+ cell count: (≤ vs. > 200 cells/mm^3) Baseline data is used to derive actual strata regardless of how they were allocated at day 1 based on screening data

Additional covariates and factors for inclusion in specific statistical models are defined as follows:

- Age (continuous covariate)
- Sex (Female vs. Male)
- Race (White, African American/African Heritage, Asian, Other)
- BMI (<25 vs. ≥ 25 kg/m2))
- Smoking status (Never vs. Former vs. Current Smoker)
- Current Vitamin D use (Yes vs. No)
- Presence of diabetes mellitus (DM) (Yes vs. No)
- Presence of hypertension (Yes vs. No)
- HIV subtype (categories will be defined from Q2 Screening lab reports): HIV subtype will have its own category if it is reported by at least 10% of subjects overall in ITT-E, the remaining subtypes will be combined into 'Others'.

Subgroups for statistical analyses and summaries by subgroup

Endpoint / Covariates and subgroups	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at week X - Snapshot algorithm by subgroup • Study Outcomes using the Snapshot algorithm by subgroup • Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL - Snapshot Analysis	• Statistical analysis of Change from baseline in CD4+ cell counts by subgroup • Summary of Change from baseline in CD4+ cell counts by subgroup	• Statistical analysis of Change from Baseline in Fasting Lipids by subgroup[2] • Summary of Change from Baseline in Fasting Lipids by subgroup[2]	• Statistical Analysis of bone biomarkers by subgroup • Summary of Bone biomarkers by subgroup	• Statistical analysis of Change from baseline in renal biomarkers by subgroup[3,4] • Summary of Change from baseline in renal biomarkers by subgroup[3,4]	• Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by subgroup • Post Baseline Adverse Events by System Organ Class, Maximum Toxicity and Subgroups
Baseline plasma HIV-1 RNA (≤ vs. >100,000, >250,000, >400,000, >500,000 c/mL)	Y					
Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL)		Y	Y	Y	Y	Y
Baseline CD4+ cell count (≤ vs. >200 cells/mm^3)	Y	Y	Y	Y	Y	Y
Age (<35, 35-<50, ≥50)	Y	Y	Y		Y	Y
Gender (Female vs. Male)	Y	Y	Y	Y	Y	Y
Race (White, African American/African Heritage, Asian, Other)	Y	Y	Y	Y	Y	Y
CDC category (Stage 0-3)	Y	Y				

Endpoint / Covariates and subgroups	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at week X - Snapshot algorithm by subgroup • Study Outcomes using the Snapshot algorithm by subgroup • Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL - Snapshot Analysis	• Statistical analysis of Change from baseline in CD4+ cell counts by subgroup • Summary of Change from baseline in CD4+ cell counts by subgroup	• Statistical analysis of Change from Baseline in Fasting Lipids by subgroup[2] • Summary of Change from Baseline in Fasting Lipids by subgroup[2]	• Statistical Analysis of bone biomarkers by subgroup • Summary of Bone biomarkers by subgroup	• Statistical analysis of Change from baseline in renal biomarkers by subgroup[3,4] • Summary of Change from baseline in renal biomarkers by subgroup[3,4]	• Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by subgroup • Post Baseline Adverse Events by System Organ Class, Maximum Toxicity and Subgroups
HIV subtype (categories will be defined from Q2 Screening lab reports)	Y	Y				
Baseline HCV serostatus (positive vs negative)	Y	Y				Y
Country	Y	Y				
BMI (<vs. ≥ 25 kg/m2)				Y		
Smoking status (Never vs. Former vs. Current Smoker)				Y		
Current Vitamin D use (Yes vs. No)				Y		
Presence of diabetes mellitus (DM)					Y	
Presence of hypertension					Y	
Age (<50, vs ≥50)	Y	Y	Y	Y	Y	Y

Endpoint / Covariates and subgroups	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at week X - Snapshot algorithm by subgroup • Study Outcomes using the Snapshot algorithm by subgroup • Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL - Snapshot Analysis	• Statistical analysis of Change from baseline in CD4+ cell counts by subgroup • Summary of Change from baseline in CD4+ cell counts by subgroup	• Statistical analysis of Change from Baseline in Fasting Lipids by subgroup[2] • Summary of Change from Baseline in Fasting Lipids by subgroup[2]	• Statistical Analysis of bone biomarkers by subgroup • Summary of Bone biomarkers by subgroup	• Statistical analysis of Change from baseline in renal biomarkers by subgroup[3,4] • Summary of Change from baseline in renal biomarkers by subgroup[3,4]	• Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by subgroup • Post Baseline Adverse Events by System Organ Class, Maximum Toxicity and Subgroups
Race (White vs. Non-White)	Y	Y	Y	Y	Y	Y
Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino	Y[1]					

[1] Only for Proportion of subjects with plasma HIV-1 RNA <50 c/mL at week X - Snapshot algorithm by subgroup

[2] Only Age (<50, vs ≥50) subgroup after week 48 will be analysed.

[3] Only baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL), baseline CD4+ cell count (≤ vs. >200 cells/mm^3), Age (<50, vs ≥50) and presence of hypertension subgroups after week 48 will be analysed.

[4] Only Serum Cystatin C, eGFR (based on CKD-EPI-creatinine and CKD-EPI-cystatin C), Urine Beta-2 Microglobulin/Urine Creatinine ratio and Urine Retinol Binding Protein/Urine Creatinine ratio after week 48 will be analysed.

10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

10.12.1. Statistical Analysis Assumptions

Analysis	Multiple imputation
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals (i.e. checking the normality assumption) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data. • Diagnostic plots (trace and autocorrelation plots) will be checked to verify that the number of burn-in iterations and MCMC steps between imputed datasets are sufficient. If the trace plots show apparent trend or the autocorrelation plots show significant positive or negative autocorrelation, number of iterations will be increased until the diagnostic plots are acceptable.	
Analysis	MMRM

• Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
• The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
• An unstructured covariance structure for the R matrix will be estimated by treatment group by specifying 'type=UN' and 'group=treat' on the REPEATED line.
  o In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
  o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
• If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.	

10.13. Appendix 13: Time to Event Details

10.13.1. TRDF Detailed Steps

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.		
Final step of the derivation is made in following order: [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. subject had CVW and discontinuation), select CVW. [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.		
Condition	**Censor Status**	**Event Description/AVAL**
1. Subjects met CVW event criteria during the randomized period. (Based on derived CVW)		
1.1 CVW event date is after the upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
1.2 CVW event date is on or before the upper bound of the analysis visit window	CNSR=0	EVNTDESC=CVW. AVAL= Study Day of SVW immediately preceding CVW.
2. Subjects with study withdrawal due to treatment related adverse events during the randomized period (defined as subjects that have reason for withdrawal =AE on disposition page and that the subject has at least one AE considered drug related (AEREL=Y) and was withdrawn from study (AEWD=Y))		

2.1 Study withdrawal is after the upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
2.2 Study withdrawal is on or before the upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Treatment Related AE. 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 Exposure domain]).
3: Subjects met protocol defined stopping criteria during the randomized period., (Based on disposition page)		
3.1 Protocol defined stopping criteria were met after the upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. 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	CNSR=0	EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria. 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 Exposure domain]).
4: Subjects with study withdrawal due to lack of efficacy during the randomized period. (Based on disposition page)		
4.1 Study withdrawal is after the upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.

4.2 Study withdrawal is on or before the upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Lack of Efficacy 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 Exposure domain])
5: If none of the above conditions met		
5.1 Subjects with study withdrawal for other reasons on or before the upper bound of the analysis visit window during the randomized period. (Based on disposition page)	CNSR=1	EVNTDESC=Censored due to Study Discontinuation for Other Reasons. 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 Exposure domain])
5.2 Subjects with study withdrawal for other reasons after the upper bound of the analysis visit window during the randomized period. (Based on disposition page)	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
5.3 Subject completed the randomized period of the study. (Based on disposition page, and Open Label completion flag)	CNSR=1	EVNTDESC= Censored as completed the Randomized Period. AVAL= Date of completion of randomized study period
5.4 Subject is ongoing in the study during the randomized period and have not yet completed the randomized period.	CNSR=1	EVNTDESC= Censored due to data cutoff. AVAL=Upper bound of analysis visit window.

10.13.2. TRDF Detailed Steps for the Kaplan-Meier plot

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: [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. subject had CVW and discontinuation), select CVW. [2] When one CENSOR (conditions 5.x) criterion is satisfied, select. 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. Subjects met CVW event criteria during the randomized period. (Based on derived CVW)	CNSR=0	EVNTDESC=CVW. AVAL=Study Day of SVW immediately preceding CVW.
2. Subjects with study withdrawal due to treatment related adverse events during the randomized period (defined as subjects that have reason for withdrawal =AE on disposition page and that the subject has at least one AE considered drug related (AEREL=Y) and was withdrawn from study (AEWD=Y))	CNSR=0	EVNTDESC=Study Withdrawal Due to Treatment Related AE. 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 Exposure domain]).
3: Subjects met protocol defined stopping criteria during the randomized period. (Based on disposition page)	CNSR=0	EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria. 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 Exposure domain]).

4: Subjects with study withdrawal due to lack of efficacy during the randomized period. (Based on disposition page)	CNSR=0	EVNTDESC=Study Withdrawal Due to Lack of Efficacy 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 Exposure domain])
5: If none of the above conditions met		
5.1 Subjects with study withdrawal for other reasons on or before the upper bound of the analysis visit window during the randomized period. (Based on disposition page)	CNSR=1	EVNTDESC=Censored due to Study Discontinuation for Other Reasons. 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 Exposure domain])
5.3 Subject completed the randomized period of the study. (Based on disposition page, and Open label completion flag)	CNSR=1	EVNTDESC= Censored as completed the Randomized Period. AVAL= Date of completion of randomized study period
5.4 Subject is ongoing in the study during the randomized period and have not yet completed the randomized period	CNSR=1	EVNTDESC= Ongoing in the Study. AVAL=Last visit date

Notes:

Randomized Period = Double-blind Randomized Phase (Day 1 to Week 96) + Open-Label Randomized Phase (Week 96 to Week 148); 'completed the randomized period' is defined as having nominal week148 date or having overall study as 'Completed' or continuation phase treatment start date is not missing or enrolled into continuation phase.

If the study day of randomized study period completion date or the last visit date is greater than day 1078, it will be censored to day 1078.

Efficacy visit windows should be used throughout for the upper bound of the analysis visit window

Subjects are considered to have completed the randomized period if they completed the Open-label Randomised Phase including the Week 148 visit

By definition, a subject 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, 48, 96, 144 – for the table analysis

Overall – for the Kaplan-Meier plot

10.13.3. ERDF Detailed Steps

Similar algorithm will be applied for ERDF analyses and Kaplan-Meier figure, where condition 2 and 3 in Section10.13.1 and Section 10.13.2 will not be considered.

10.13.4. Time to Viral Suppression

- Time of event will be the first on-treatment viral load value <50 copies/mL
- Subjects who withdraw for any reason without being suppressed during on treatment will be censored at earliest of (day of study discontinuation, day of withdrawal visit, day of treatment discontinuation).
- Subjects who have not been withdrawn and have not had viral suppression at time of the analysis will be censored at last viral load date from HIV-1RNA lab data.
- Subjects who have completed the Double Blind and Open Label phases and have not had viral suppression will be censored at date of completion.

10.14. Appendix 14: Q2 Creatinine Assay Accuracy Issue

10.14.1. Q2 Creatinine Assay Accuracy Issue

There was an issue with the Q2 instrument at the Valencia site (in California) measuring serum creatinine concentrations between 1-Oct-2106 and 13-Jan-2017 resulting in some serum creatinine values being unreliable. The unreliable serum creatinine samples will be excluded from the summaries. The erroneous samples will be flagged in the listings. The samples can be identified in SDTM.LB by searching for the following comment: "SERUM CREATININE WAS PRODUCED DURING AN INTERMITTENT INSTRUMENT MALFUNCTION FROM 01OCT16 TO 13JAN17 AT Q2 SOLUTIONS, VALENCIA. THE SERUM CREATININE RESULT REPORTED IS POTENTIALLY ERONEOUS".

10.15. Appendix 15: Abbreviations & Trade Marks

Abbreviations

Abbreviation	Description
3TC	Lamivudine, EPIVIR
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
ART	Antiretroviral therapy
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COM	Comparator arm
CSR	Clinical Study Report
CVW	Confirmed Virologic Withdrawal
D3	DTG + 3TC arm
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FDC	Fixed-dose combination
FTC	Emtricitabine
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-To-Treat
LOCF	Last Observation Carries Forward
PP	Per Protocol
QC	Quality Control
PPD	Pharmaceutical Product Development
RAP	Reporting & Analysis Plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
TD	Target Detected
TDF	Tenofovir disoproxil fumarate
TFL	Tables, Figures & Listings
TND	Target Not Detected
GSK	GlaxoSmithKline

Trademarks

Trademarks of ViiV Healthcare
Epivir
Tivicay

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Monogram Inc
PhenoSense
SAS
Truvada

10.16. Appendix 16: End of Study (Final) Analysis

This appendix will provide the details of planned analyses and data displays for the End of Study (EOS; final) reporting. These analyses may be included in regulatory submissions, study reports and publications.

10.16.1. General considerations for data analyses

This section is written specifically for the EOS analysis. Since the primary analyses have been completed, the present section is written to cover only analyses included in the final reporting. Only those definitions and derivations that have changed since the previous interim and primary analyses will be included in this section, i.e., for the derivation of analysis windowing, how to deal with missing dates, definition of concomitant medications, etc. refer to the previous corresponding RAP sections. The current section summarizes only the key endpoints of interest for the final analysis and explains any deviations from the previous analysis.

The details of the final EOS reporting and analysis are described below:

1) The analysis for which the data have not been changed since the last interim analysis (Week 144 analysis) will not be reported to avoid redundancy.

2) No subgroup analysis, hypotheses testing, or statistical analyses will be performed.

3) As per the Time and Events Schedule health outcomes will not be reported for EOS.

4) All required disclosure outputs following the FDAAA and EudraCT guidelines will be produced.

5) For the purpose of creation of Mexico Final Safety Report and submission to Ministry of Health, some listings at Mexico sites will be reported separately. Such listings are identified in the Programming notes in Section 10.16.7. These listings will include data from both Randomized and Continuation Phase.

10.16.1.1. Study Phases

In the previous analysis (Week 144 analysis), data were summarized for the Double Blinded and Open Label Phases of the study. However, when data from the Continuation Phase were available, Continuation Phase was also included. For the EOS reporting, data to be analysed/ reported are from Continuation Phase unless specified otherwise, and this will be noted in the title of the output. Listings will contain all the data with a new column added to specify the phase of the study for each record. Continuation Phase is defined as below:

Phase	Start	End
Continuation Phase	Week 148 (start date of exposure where category of treatment is 'CONTINUATION PHASE'.	Study completion/discontinuation date

Note: A participant enters the Continuation Phase if they have at least one exposure to the Investigational Product after analysis visit Week 148.

Due to issues with approval for the local post-study access program in GEMINI-II during the pandemic, total 10 Peru DTG + TDF/FTC participants continued treatment for up to 1 year post week 148. These subjects' post week 148 visits will be in Continuation Phase. Their data will be included in the listings, but not in the summary tables.

10.16.1.2. Analysis Population for the Continuation Phase

In addition to the populations defined in Section 4 of the RAP amendment 2, the following populations were defined for the End of Study Analysis:

Population	Definition/ Criteria.	Analysis Evaluated
Safety Continuation	Comprises all participants in the Safety Population who receive at least one dose of Investigational Product after entering the Continuation Phase.	• Safety
CVW Continuation	Comprise of all subjects in the ITT-E population who have met the derived CVW criteria during the Continuation Phase.	• Efficacy • Study Population
Intent-to-Treat Exposed (ITT-E) Continuation	Comprises all participants in the ITT-E Population who enter the Continuation Phase.	• Efficacy • Study Population
Viral Genotypic Continuation	Comprises all participants in the ITT-E Population with available on-treatment genotypic resistance data during the Continuation Phase	• Genotypic
Viral Phenotypic Continuation	Comprises all participants in the ITT-E- Population with available on-treatment phenotypic resistance data during the Continuation phase	• Phenotypic

10.16.2. Study Population

The study population summaries and data listings will be based on the ITT-E or ITT-E Continuation Population, unless otherwise specified. Demographic and baseline

characteristics will be reported only for the subjects who entered the Continuation Phase. Participant accountability summary will be produced for the Continuation Population.

Overview of the key planned study population endpoints:

- Study Populations
- Summary of Number of Subjects Enrolled by Country and Site ID for the Continuation Population.
- Participant Accountability
- Concomitant and Antiretroviral Medications.
- Protocol deviation.

Full details of the data displays are given in Section 10.16.7.

10.16.3. Efficacy Analysis

The efficacy summaries and data listings will be based on the ITT-E Continuation Population.

Overview of the key planned efficacy endpoints:

- Proportion of Participants with Plasma HIV-1 RNA < 50 c/ mL observed data
- Proportion of Participants with Confirmed Virologic Withdrawal – observed data
- Change from baseline CD4+ cell count over time
- Incidence of disease progression and HIV-associated conditions

Full details of data displays are given in Section 10.16.7.

10.16.4. Safety Analysis

All safety displays will be based on the Safety Population or the Safety Continuation Population.

The core adverse event displays for the final report have been identified based on the IDSL library required tables. For the purposes of summarising the AE data (including COVID-19), unless stated otherwise, the summaries will include only those AEs that occurred during the Continuation Phase. Common AEs are those with 2% (without rounding) incidence for any treatment.

Summaries of AEs required for the FDAAA and EudraCT will be generated in this report.

Summaries of Maximum Post-Baseline Grade 3 or 4 Emergent Clinical Toxicities and Hepatobiliary Abnormality criteria will be reported only for the events that occurred during the Continuation Phase.

A new figure of cumulative exposure to investigational product will be added for the Continuation Phase.

Overview of the key planned safety endpoints:

- Extent of Exposure
- Adverse Events

- Maximum Post-Baseline Emergent Clinical Chemistry/ Haematology Toxicities
- Hepatobiliary Laboratory Abnormality Criteria
- Liver Events Assessment
- Columbia Suicidality Severity Rating Scale (C-SSRS)

Full details of data displays are given in Section 10.16.7.

10.16.5. Virology analysis

The virology summaries will be based on the Viral Genotypic and Viral Phenotypic Continuation Populations, unless otherwise specified. Data listings will be presented for the ITT-E Continuation Population, unless otherwise specified.

Prespecified lists of integrase substitutions have been modified since the previous interim analysis, hence an updated list of known INSTI mutations has been added in Table 8 and IAS-USA major resistance associated mutations (RAMs) to other classes (i.e., NRTI, NNRTI, PI) are listed in Table 9.

Table 8 Known INSTI mutations associated with the development of resistance to RAL, BIC, EVG or DTG

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A/I/K**, L74M, **E92Q/V**/G, Q95K, T97A, G118R, **F121Y**, E138A/K, G140A/C/S, **Y143C/H/R/K/S/G/A**, **P145S**, **Q146P**, **S147G**, **Q148**N/**H/K/R**, **V151**I/**L**/A, S153F/Y, **N155H**/S/T, E157Q, G163R/K, S230R, R263K, L68V/I*, L74I*, E138T*, 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.
- INSTI mutations in bold have the maximum score of 60 and are for any INSTI drug in the Stanford database v9.1 (https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/, last updated on 2022-06-02); the rest have a maximum score <60.
- The INSTI mutations listed are historically identified via the Stanford HIV Resistance database, and also include mutations identified during in vitro passage of DTG, or as seen in a previous DTG study in INI-experienced participants (ING112574).

Table 9 Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) as defined by the International Antiviral Society-USA (IAS-USA)

Class	Mutations
NRTIs	M41L, K65R/E/N, D67N, 69 insert, K70E/R, L74V, Y115F, M184V/I, L210W, T215Y/F, K219Q/E; [A62V, V75I, F77L, F116Y, Q151M]
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, M230I/L
PIs	D30N, V32I, M46I/L, I47A/V, G48V, I50V/L, I54V/M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S, L90M

NOTES:

- Updated to "2019 Resistance Mutations Update Volume 27 Issue 3, July/August 2019
- The most up to date IAS-USA guidelines available at the time of DBF will be used in the analysis.
- Q151M Complex: Q151M usually occurs in combination with two or more of the following four accessory NRTI mutations A62V, V75I, F77L, and F116Y However if any one of these mutations occur alone, they shall be considered as major mutation for the NRTI class.

Overview of the key planned virology endpoints:

- Genotypic and Phenotypic Accountability
- INSTI mutations
- Major NRTI, NNRTI, PI mutations
- Fold Change
- Fold Change Ratio

Full details of data displays are given in Section 10.16.7.

10.16.6. COVID - 19 analysis

This study was started in 2016 and continued during the COVID -19 pandemic. The information regarding the number of participants affected by COVID-19 and its symptoms will be reported according to GSK core standards. The visits impacted due to the pandemic outbreak will be reported. Protocol deviations or adverse events related to COVID-19 if any, will also be reported according to GSK core standards.

If the subjects have competed /withdrawn the study before the pandemic started in the respective countries according the COVID-19 dataset (with start date of pandemic in each of the countries), they will be considered as 'Not Related' to COVID-19.

10.16.7. List of Data Displays for End of Study (EOS) Final Report

- Outputs that were not reported in previous reporting effort are identified in Programming Notes as 'New output'.

Study Population					
Type	**No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Table	1.101	ITT-E Continuation	Same shell as week 144, table 1.1	Summary of Number of Subjects Enrolled by Country and Site ID	
Table	1.102	All Subjects Screened	SA1	Summary of Study Populations	CS CORE; Present all populations as defined in Sections 4 and 10.16.1.2
Table	1.103	ITT-E	ES1	Summary of Subject Status and Subject Disposition by Relationship to COVID-19 Pandemic - Overall	FDAAA, EudraCT For overall, Summarise by: i) Overall ii) Related to COVID-19, ii) Not Related to COVID-19
Table	1.104	ITT-E Continuation	ES1	Summary of Subject Status and Subject Disposition by Relationship to COVID-19 Pandemic - Continuation Phase	New Output; FDAAA, EudraCT For Continuation Phase Summarise by: i) Overall ii) Related to COVID-19, ii) Not related to COVID-19
Table	1.105	ITT-E Continuation	DM1	Summary of Demographic Characteristics	
Table	1.106	ITT-E Continuation	DV1a	Summary of Important Protocol Deviations by Relationship to COVID-19 Pandemic - Continuation Phase	CS CORE
Table	1.107	ITT-E Continuation	CM1	Summary of Concomitant Medication by ATC Level 1 and Ingredient – Continuation Phase	
Listing - ICH	101	ITT-E Continuation	ES2	Listing of Study Conclusions Reasons for Study Withdrawal – Continuation Phase	CS CORE
Listing - ICH	102	ITT-E Continuation	DV2	Listing of Important Protocol Deviations – Continuation Phase	CS CORE

Listing - Other	103	ITT-E Continuation	Same shell as week144, listing 32	Listing of Visit Dates	Include all visits
Listing - Other	104	All Participants Screened	Same shell as week144, listing 33	Listing of Study Populations	
Listing - Other	105	ITT-E Continuation	CM2	Listing of Concomitant Medications – Continuation Phase	
Listing - Other	106	ITT-E Continuation	CM6	Listing of Relationship Between ATC Level 1, Ingredient and Verbatim Text – Continuation Phase	
Listing - Other	107	ITT-E Continuation	CM2	Listing of Concomitant ART Medications – Continuation phase	
Listing - Other	108	ITT-E Continuation	CM6	Listing of Relationship Between ATC Level 4, Ingredient and Verbatim Text – Continuation Phase	

Efficacy					
Type	**No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Table	2.101	ITT-E Continuation	Same shell as week 48, table 2.15	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit -Observed Data	Include all visits
Table	2.102	ITT-E Continuation	Same shell as week 48, table 2.16	Summary of Change from Baseline in Plasma HIV-1 RNA (log10 c/mL) by Visit	Include all visits
Table	2.103	CVW Continuation	Same shell as week 144, table 2.18	Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit by Type of Criteria	Proportion instead of 'Cumulative Proportion' comparing to previous REs. Include all visits
Table	2.104	CVW Continuation	Same shell as week 144, table 2.19	Distribution of Quantitative Plasma HIV-1 RNA Results at Suspected and Confirmed Virologic Withdrawal	Data only for the subjects that meet CVW. We want to know how the CVW subjects' viral loads changed from the SVW to CVW visit.. Include all visits
Table	2.105	ITT-E Continuation	Same shell as week 144, table 2.22	Summary of Change from Baseline in CD4+ Cell Count (cells/mm^3) by Visit	Include all visits
Table	2.106	ITT-E Continuation	Same shell as week 144, table 2.25	Summary of Post-Baseline HIV-1 Associated Conditions Including Recurrences - Continuation Phase	
Table	2.107	ITT-E Continuation	Same shell as week 144, table 2.26	Summary of Post-Baseline HIV-1 Associated Conditions Excluding Recurrences – Continuation Phase	
Table	2.108	ITT-E Continuation	Same shell as week 144, table 2.27	Summary of Post-Baseline HIV-1 Disease Progressions - Continuation Phase	
Figure	2.101	ITT-E Continuation	Same shell as week 144, figure 2.3	Individual Plasma HIV-1 RNA and CD4+ Profiles by Visit for Subjects with at least One Suspected Virologic Withdrawal Visit	Include all visits
Listing - ICH	201	ITT-E Continuation	Same shell as week 144, listing 12	Listing of Quantitative and Qualitative Plasma HIV-1 RNA Data	Include all visits

Listing - Other	202	ITT-E Continuation	Same shell as week 144, listing 50	Listing of Plasma HIV-1 RNA Data for Subjects with Confirmed Virologic Withdrawal	Include all visits
Listing - Other	203	ITT-E Continuation	Same shell as week 144, listing 51	Listing of CD4+ Cell Count Data	Include all visits
Listing - Other	204	ITT-E Continuation	Same shell as week 144, listing 52	Listing of HIV-1 Associated Conditions - Continuation Phase	

Safety					
Type	**No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Table	3.101	Safety Continuation	EX1	Summary of Extent of Exposure to Investigational Product for Subjects who Entered Continuation Phase	Including all phases
Table	3.102	Safety Continuation	AE3	Summary of Common (>=2%) Adverse Events by Preferred Term and Overall Frequency - Continuation Phase	Common adverse events are those with >=2% (without rounding) incidence for any treatment.
Table	3.103	Safety Continuation	AE3	Summary of Common (>=2%) Grade 2-5 Adverse Events by Preferred Term and Overall Frequency - Continuation Phase	
Table	3.104	Safety Continuation	AE5A	Summary of All Drug-related Adverse Events by System Organ Class, Preferred Term and Maximum Toxicity - Continuation Phase	
Table	3.105	Safety Continuation	AE3	Summary of Common (>=1%) Drug-related Grade 2-5 Adverse Events by Overall Frequency - Continuation Phase	
Table	3.106	Safety Continuation	AE3	Summary of Serious Adverse Events by System Organ Class and Preferred Term - Continuation Phase	
Table	3.107	Safety Continuation	AE15	Summary of Common (>=2%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Continuation Phase	FDAAA, EudraCT Common adverse events are those with >=2% (without rounding) incidence for any treatment.
Table	3.108	Safety Continuation	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Continuation Phase	FDAAA, EudraCT
Table	3.109	Safety Continuation	PAN1A	Summary of COVID-19 Assessments for Subjects with Suspected, Probable or Confirmed COVID-19 Case Diagnosis – Continuation Phase	New output. Please refer to Sailing EOS T8.26
Table	3.110	Safety Continuation	PAN3A	Summary of COVID-19 Symptoms for Subjects with Suspected, Probable or Confirmed COVID-19 Case Diagnosis – Continuation Phase	New output. Please refer to Sailing EOS T8.27
Table	3.111	Safety Continuation	Same shell as week 144, table 3.55	Summary of Maximum Post-Baseline Emergent Clinical Chemistry Toxicities - Continuation Phase	

Table	3.112	Safety Continuation	Same shell as week 144, table 3.56	Summary of Maximum Post-Baseline Emergent Hematology Toxicities - Continuation Phase	
Table	3.113	Safety Continuation	Same shell as week 144, table 3.57	Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria - Post-Baseline Emergent - Continuation Phase	
Table	3.114	Safety Continuation	Same shell as week 144, table 3.58	Summary of True Positive Suicidal Indication/ Behaviour Alerts based on eCSSRS by Visit – Continuation Phase	
Table	3.115	Safety Continuation	Same shell as week 144, table 3.60	Summary of Subjects with Post-Baseline C-SSRS Suicidal Ideation or Behaviour – Continuation Phase	
Table	3.116	Safety Continuation	Same shell as week 144, table 3.2	Summary of All Adverse Events by System Organ Class and Preferred Term – Continuation Phase	
Table	3.117	Safety Continuation	Same shell as week 144, table 3.3	Summary of All Adverse Events by Maximum Grade – Continuation Phase	
Figure	3.101	Safety Continuation	Same shell as week 144, figure 3.3	Scatter Plot of Maximum Post-Baseline ALT vs. Maximum Post-Baseline Total Bilirubin - Continuation Phase	
Figure	3.102	Safety Continuation	gsk1349572/ing111762/final_01/figure 8.27	Plot of Cumulative Exposure to Investigational Product	Include all visits
Listing - ICH	301	Safety Continuation	HIV_IP5/ EX3	Listing of Investigational Product Exposure Data	
Listing - ICH	302	Safety Continuation	AE8	Listing of All Adverse Events	Listing all AEs for the subjects in Safety Continuation & Include 'study phase'
Listing – ICH	303	Safety Continuation	AE8	Listing of Fatal Serious Adverse Events – Continuation Phase	
Listing - ICH	304	Safety Continuation	AE8	Listing of Non-Fatal Serious Adverse Events – Continuation Phase	
Listing - ICH	305	Safety Continuation	AE8	Listing of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product – Continuation Phase	
Listing - Other	306	Safety	AE8	Listing of Non-Serious AEs of Subjects at Mexico Sites	
Listing - Other	307	Safety	AE8	Listing of SAEs of Subjects at Mexico Sites	
Listing - Other	309	Safety Continuation	Same shell as week 144, listing 63	Listing of Post Baseline Maximum ALT and Maximum Bilirubin – Continuation Phase	
Listing - Other	310	Safety Continuation	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting – Continuation Phase	

Listing - Other	311	Safety Continuation	Same shell as week 144	Listing of Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Criteria -Continuation Phase	
Listing - Other	312	Safety Continuation	PREG1a	Listing of Subjects Who Became Pregnant During the Study – Continuation Phase	
Listing - Other	313	Safety Continuation	LB5	Listing of Laboratory Data for Subjects with Grade 3 or 4 Post-Baseline Emergent Toxicities – Continuation Phase	
Listing - Other	314	Safety Continuation	PAN12	Listing of COVID-19 Assessments and Symptoms Assessments for Subjects with COVID-19 Adverse Events – Continuation Phase	New output

Virology					
Type	**No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Table	4.101	Viral Genotypic Continuation	Same shell as week144, table 4.1	Summary of Subject Accountability: Genotypes Available	
Table	4.102	Viral Phenotypic Continuation	Same shell as week144, table 4.2	Summary of Subject Accountability: Phenotypes Available	
Table	4.103	Viral Genotypic Continuation	PFG1	Summary of Major Mutations in NNRTI, NRTI and PI Classes and Pre-specified Mutations in INSTI Class at Baseline and time of CVW for Subjects Meeting CVW Criteria	
Table	4.104	Viral Genotypic Continuation	Same shell as week144, table 4.7	Summary of S-GSS at Time of CVW by Genotypic Cut-Off for DTG and 3TC - Continuation Phase	
Table	4.105	Viral Phenotypic Continuation	Same shell as week144, table 4.8	Summary of Phenotype at Time of CVW by Phenotypic Cut-off - Continuation Phase	
Table	4.106	Viral Phenotypic Continuation	Same shell as week144, table 4.9	Number of Drugs to Which Subjects are Phenotypically Resistant at Time of CVW – Continuation Phase	
Table	4.107	Viral Phenotypic Continuation	Same shell as week144, table 4.10	Summary of Fold Change to DTG, 3TC, TDF and FTC at Time of CVW - Continuation Phase	
Listing - Other	401	ITT-E Continuation	Same shell as week144, listing 79	Listing of All Genotypic Data	
Listing - Other	402	Viral Genotypic Continuation	Same shell as week144, listing 80	Listing of Treatment Emergent Genotypic Mutations – Continuation Phase	
Listing - Other	403	Viral Genotypic Continuation	Same shell as week144, listing 81	Listing of Genotype by Genotypic Cut-Off – CVWs	
Listing - Other	404	ITT-E Continuation	Same shell as week144, listing 82	Listing of All Phenotypic Data	
Listing - Other	405	Viral Phenotypic Continuation	Same shell as week144, listing 84	Listing of Net Assessment Score – CVWs	
Listing - Other	406	Viral Genotypic and/or Phenotypic Continuation	Same shell as week144, listing 85	Listing of Genotypic and Phenotypic Data for Subjects with Confirmed Virologic Withdrawal Criteria	
Listing - Other	407	ITT-E Continuation	Same shell as week144, listing 86	Listing of Genotypic and Phenotypic Data for Subjects with On-treatment Virology Results at Non-CVW Timepoints	
Listing - Other	408	ITT-E Continuation	Same shell as week144, listing 87	Listing of Subject Level Summary of Key Virologic Data for Subjects with Confirmed Virologic Withdrawal or On-Treatment Non-CVW Timepoints - Continuation Phase	

10.17. Appendix 17: List of Data Displays

10.17.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Genotype and Phenotype	4.1 to 4.n	4.1 to 4.n
Heath Outcomes	5.1 to 5.n	5.1 to 5.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.17.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided. Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in a separate document. Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Genotype and Phenotype	Viral_Fn	Viral_Tn	CVW_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.17.3. Deliverables

Delivery [1]	Description
Datalook	During Study
24	Statistical Analysis Complete at Week 24
48	Statistical Analysis Complete at Week 48
96	Statistical Analysis Complete at Week 96
144	Statistical Analysis Complete at Week 144
EOS	Final End of Study Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

10.17.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Subjects Screened	NS1	Summary of Number of Subjects Enrolled by Country and Site ID	CS CORE	All
1.2.	All Subjects Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	CS CORE; add subreason, i.e # of IE criteria	All
1.3.	ITT(E)	ES1	Summary of Subject Disposition for the Subject Conclusion Record		All
1.4.	ITT(E)	ES1	Summary of Subject Disposition for the Subject Conclusion Record: Double Blind Phase		All
1.5.	ITT(E)	ES1	Summary of Subject Disposition for the Subject Conclusion Record: Open Label Phase		All
1.6.	ITT(E)	HIV_ES1 or SD4 or SD1 or ISO4	Summary of Reasons for Withdrawal by Visit		All
Study populations					
1.7.	All Subjects Screened	SP1	Summary of Study Populations		All
1.8.	ITT(E)	shell	Summary of misrandomized strata or treatment		All
Protocol deviations					
1.9.	ITT(E)	DV1	Summary of Important Protocol Deviations	CS CORE	All
1.10.	ITT(E)	SA2	Summary of Protocol Deviations Leading to Exclusion from the Per-Protocol Population	CS CORE	All

Demography					
1.11.	ITT(E)	DM1	Summary of Demographic Characteristics	CS CORE	All
1.12.	All Subjects Screened	DM11	Summary of Age Ranges		All
1.13.	ITT(E)	DM5	Summary of Race and Racial Combinations	CS CORE	All
1.14.	ITT(E)	DM6	Summary of Race and Racial Combinations Details	CS CORE	All
1.15.	ITT(E)	shell	Summary of Hepatitis Status at Entry		All
1.16.	ITT(E)	CDC1	Summary of CDC Classification of HIV Infection at Baseline		All
1.17.	ITT(E)	RF1	Summary of HIV Risk Factors		All
1.18.	ITT(E)	shell	Summary of Screening Cardiovascular Risk Assessments		All
1.19.	ITT(E)	shell	Distribution of Quantitative Plasma HIV-1 RNA Results at Screening and Baseline		All
1.20.	ITT(E)	shell	Distribution of CD4+ Cell Count (cells/mm^3) Results at Screening and Baseline		All

Medical Conditions, Concomitant Medications & ART					
1.21.	ITT(E)	MH1	Summary of Current Medical Conditions	CS CORE	All
1.22.	ITT(E)	MH1	Summary of Past Medical Conditions	CS CORE	All
1.23.	ITT(E)	MH4	Summary of Current Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		All
1.24.	ITT(E)	MH4	Summary of Past Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		All
1.25.	ITT(E)	CM1	Summary of Concomitant Medication by Ingredient ATC Level 1		All
1.26.	ITT(E)	CM8	Summary of Concomitant Medication by Ingredient Combinations		All
1.27.	ITT(E)	CM1b	Summary of Concomitant Medication by Combination Term ATC Level 1		All
1.28.	ITT(E)	shell	Summary of Lipid Modifying Agent Use at Baseline		All
1.29.	ITT(E)	shell	Summary of Lipid Modifying Agent Use Starting Post-Baseline		All
1.30.	ITT(E)	shell	Summary of History of Depression and Anxiety at Baseline		All
1.31.	ITT(E)	shell	Number of Subjects Attending Nominal and Actual Analysis Visits		Week 48, 96, 144

10.17.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Primary Efficacy Analyses					
2.1.	ITT(E)	Shell gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X – Snapshot Analysis		All
2.2.	Per-Protocol	Shell	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X – Snapshot Analysis		All
2.3.	ITT	Shell	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X – Snapshot Analysis		All
2.4.	ITT(E)	Shell gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week X – Snapshot Analysis		All
2.5.	Per-Protocol	Shell	Summary of Study Outcomes (<50 c/mL) at Week X – Snapshot Analysis		All
2.6.	ITT	shell	Summary of Study Outcomes (<50 c/mL) at Week X – Snapshot Analysis		All
2.7.	ITT(E)	Shell gsk2619619/ing117172/week48/drivers/t_snap_sum_prop_p.sas	Treatment by Strata Tests of Homogeneity for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X - Snapshot Analysis		All

2.8.	ITT(E)	Shell gsk2619619/ing117172/week48/drivers/t_ef_km_trdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal at Week X - Treatment Related Discontinuation = Failure Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups		All
2.9.	ITT(E)	Shell gsk2619619/ing117172/week48/drivers/t_ef_km_erdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal at Week X - Efficacy Related Discontinuation = Failure Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups		All
2.10.	ITT(E)	shell	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 using Snapshot - bias Sensitivity Analysis		Wk48
Secondary Efficacy Analyses					
Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL – Snapshot					
2.11.	ITT(E)	shell	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit - Snapshot Analysis		All
2.12.	ITT(E)	shell	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X by Subgroup – Snapshot Analysis – ITT-E	See subgroups in Section 10.11 plus categories for Baseline plasma HIV-1 RNA (c/mL) - <= 100K, > 100K, >250K, >400K and >500K (add the last 3 more categories as in Table 8.3 mid208959/postcsr_2018_01)	All
2.13.	ITT(E)	shell	Summary of Study Outcomes (<50 c/mL) at Week X by Subgroup - Snapshot Analysis		All

Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL – Observed					
2.16.	ITT(E)	shell	Summary of Change from Baseline in Plasma HIV-1 RNA (log10 c/mL) by Visit		All
Kaplan - Meier					
2.17.	ITT(E)	shell or Table 6.5 mid208959/present_2018_03	Statistical Analysis of Kaplan-Meier Estimates of Time to Viral Suppression Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups	Add categories: Baseline HIV-1 RNA (c/mL) <= 100,000 vs. > 100,000 for WK 96 onwards	All
Confirmed Virologic Withdrawal (CVW)					
2.18.	ITT(E)	Shell	Cumulative Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit by Type of Criteria		All
2.19.	ITT(E)	Shell	Distribution of Quantitative Plasma HIV-1 RNA Results at Suspected and Confirmed Virologic Withdrawal	Data only for the subjects that meet CVW. We want to know how the CVW patients viral loads changed from the SVW to CVW visit.	All
CD4+ Cell Counts					
2.20.	ITT(E)	shell	Statistical Analysis of Change from Baseline in CD4+ Cell Count (cells/mm^3) at Week X - (Multiple imputed Dataset - MAR)		Week 24, 48
2.21.	ITT(E)	shell	Statistical Analysis of Change from Baseline in CD4+ Cell Count (cells/mm3) - MMRM	use similar mock shell such as fasting lipids, just change to reflect CD4 endpoint	All

2.22.	ITT(E)	Shell gsk2619619/ing117172/week48/drivers/ef_t_cd4_chg.sas	Summary of Change from Baseline in CD4+ Cell Count (cells/mm^3) by Visit		All
2.23.	ITT(E)	shell	Summary of Change from Baseline in CD4+ Cell Count (cells/mm^3) at Week X by Subgroup	See subgroups in Section 10.11	All
2.24.	ITT(E)	shell	Statistical Analysis of Change from Baseline in CD4+ Cell Count by subgroup (cells/mm^3) at Week X– Observed case	See subgroups in Section 10.11	All
Post-baseline HIV-1 Disease Progression					
2.25.	ITT(E)	shell	Summary of Post-Baseline HIV-1 Associated Conditions Including Recurrences		All
2.26.	ITT(E)	shell	Summary of Post-Baseline HIV-1 Associated Conditions Excluding Recurrences		All
2.27.	ITT(E)	shell	Summary of Post-Baseline HIV-1 Disease Progressions		All
Additional Subgroup Analysis					
2.28.	PP	shell (Table 2.12)	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X by Subgroup - Snapshot Analysis - PP		Week 48, 96, 144
2.29.	ITT(E)	shell (Table 2.14)	Summary of Study Outcomes (<50 c/mL) at Week X by Baseline Plasma HIV-1 RNA and CD4+ Cell Count - Snapshot Analysis	Only one category of most severe subjects	Week 48, 96,
Proportion of Subjects with Plasma HIV-1 RNA <40 copies/mL – Snapshot					
2.33.	ITT(E)	shell (Table 2.11)	Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL by Visit - Snapshot Analysis		Week 48, 96, 144

2.34.	ITT(E)	Table 2.34 mid208959/ primary_02	Summary of CD4+ Cell Count (cells/mm3) by Visit		Week 48 (ad hoc), 96, 144
2.41.	ITT(E)	Table 9.1 mid208959/ postcsr_2018_02	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week x by Baseline Plasma HIV-1 RNA and CD4+ Cell Count - Snapshot Analysis – ITTE	Only one category of most severe subjects	Week 96
2.42.	PP	Table 9.2 mid208959/ postcsr_2018_02	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week x by Baseline Plasma HIV-1 RNA and CD4+ Cell Count - Snapshot Analysis - PP	Only one category of most severe subjects	Week 96
2.43.	ITT(E)	mid208959/ present_2018_03	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL at Week X - Snapshot Analysis - ITT-E		Week 96, 144
2.44.	ITT(E)	mid208959/ present_2018_03	Summary of Study Outcomes (<40 c/mL) at Week X - Snapshot Analysis - ITT-E		Week 96, 144
2.45.	ITT(E)	mid208959/ present_2018_03	Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL at Week X by Subgroup - Snapshot Analysis - ITT-E		Week 96, 144

10.17.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Efficacy					
2.1.	ITT(E)	shell	Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL by Visit – Snapshot Analysis	Line plot	All
2.2.	ITT(E)	shell	Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week X by Subgroup – Snapshot Analysis		All
2.3	ITT(E)	shell	Individual Plasma HIV-1 RNA and CD4+ Profiles by Visit for Subjects with at least One Suspected Virologic Withdrawal Visit		All
2.4	ITT(E)	shell	Kaplan-Meier Plot of Time to Failure - Treatment related discontinuation = Failure (TRDF)		All
2.5	ITT(E)	shell	Kaplan-Meier Plot of Time to Failure - Efficacy related discontinuation = Failure (ERDF)		All
2.6	ITT(E)	shell Table 6.2 mid208959/present_2018_03	Kaplan-Meier Plot of Time to Viral Suppression Overall and by Baseline HIV-1 RNA and CD4+ Cell Count Subgroups	add categories: Baseline HIV-1 RNA (c/mL) <= 100,000 vs. > 100,000	All
2.7	ITT(E)	shell	Line Plot of Adjusted Mean (95% CI) Change From Baseline in CD4+ Cell Count (cells/mm^3) Over Time – Repeated Measure Mixed Model		All

10.17.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
3.1.	Safety	EX1	Summary of Extent of Exposure to Investigational Product Including Continuation Phase	CS Core	All, title update for Week 148
Adverse Events					
3.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	CS Core	All
3.3.	Safety	AE5A	Summary of All Adverse Events by Maximum Grade	CS Core	All
3.4.	Safety	AE1	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term	CS Core	All
3.5.	Safety	AE5A	Summary of Drug-Related Adverse Events by Maximum Grade	CS Core	All
3.6.	Safety	AE3	Summary of Common (>=2%) Adverse Events by Overall Frequency	CS Core	All
3.7.	Safety	AE3	Summary of Common (>=2%) Grade 2-5 Adverse Events by Overall Frequency	CS Core	All
3.8.	Safety	AE15	Summary of Common (>=2%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	CS Core	All
3.9.	Safety	AE3	Summary of Common (>=1%) Drug-Related Grade 2-5 Adverse Events by Overall Frequency	CS Core	All
3.10.	Safety	Dori	Summary of Liver Monitoring/Stopping Event Reporting		All

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.11.	Safety	AE5B	Summary of Adverse Events by System Organ Class, Maximum Toxicity and Subgroups	See subgroups in Section 10.11. Add row for each subgroup, and use corresponding number of subjects as denominator	Up to Week 96
3.13.	Safety	AE5A	Summary of Post-treatment AE by SOC and Maximum Toxicity		All
Serious and Other Significant AEs					
3.14.	Safety	AE1	Summary of Fatal Adverse Events	CS Core	All
3.15.	Safety	AE1	Summary of Drug-Related Fatal Adverse Events	CS Core	All
3.16.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class		All
3.17.	Safety	AE3	Summary of Serious Drug-Related Adverse Events by Overall Frequency	Plain Language Summary (PLS) requirements	All
3.18.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		All
3.19.	Safety	AE1 or AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		All
3.20.	Safety	AE1 or AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by subgroup	See subgroups in Section 10.11	Up to Week 96

Special Interest AEs					
3.21.	Safety	Shell	Summary of Characteristics of Rash Adverse Events of Special Interest		All
3.22.	Safety	Shell	Summary of Onset and Duration of the First Occurrence of Rash Adverse Events of Special Interest		All
3.23.	Safety	Shell	Summary of Total Duration of Rash Adverse Events of Special Interest		Up to Week 96
3.24.	Safety	Shell	Summary of Characteristics of Hypersensitivity Adverse Events of Special Interest		All
3.25.	Safety	Shell	Summary of Onset and Duration of the First Occurrence of Hypersensitivity Adverse Events of Special Interest		All
3.26.	Safety	Shell	Summary of Total Duration of Hypersensitivity Adverse Events of Special Interest		Up to Week 96
3.27.	Safety	Shell	Summary of Characteristics of Insomnia Adverse Events of Special Interest		All
3.28.	Safety	Shell	Summary of Onset and Duration of the First Occurrence of Insomnia Adverse Events of Special Interest		All
3.29.	Safety	Shell	Summary of Total Duration of Insomnia Adverse Events of Special Interest		Up to Week 96
3.30.	Safety	Shell	Summary of Characteristics of Nightmare / Abnormal Dreams Adverse Events of Special Interest		All
3.31.	Safety	Shell	Summary of Onset and Duration of the First Occurrence of Nightmare / Abnormal Dreams Adverse Events of Special Interest		All
3.32.	Safety	Shell	Summary of Total Duration of Nightmare / Abnormal Dreams Adverse Events of Special Interest		Up to Week 96

Laboratory Values Over Time					
3.33.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit		All
3.34.	Safety	shell	Statistical analysis of Change from Baseline in Fasting Lipids at Week X (Multiple imputed Dataset - MAR)		Week 24, 48
3.35.	Safety	shell	Table 3.351 Statistical analysis of Change from Baseline in Fasting Lipids at Week X - MMRM-Lipid LOCF Table 3.352 Statistical analysis of Change from Baseline in Fasting Lipids at Week X – Loge Transformed Data – MMRM - Lipid LOCF		All, add table 3.352 for WK 148
3.36.	Safety	LB1	Summary of Lipids Percentage Changes from Baseline by Visit		Up to Week 96
3.37.	Safety	LB1	Summary of Hematology Changes From Baseline by Visit		All
3.38.	Safety		Summary of Urine Concentrations Changes from Baseline by Visit		All
3.39.	Safety	shell	Summary of Changes in TC/HDL ratio Category to Maximum Post-Baseline Category		Up to Week 96
3.40.	Safety	shell	Statistical analysis of Maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Week X		All
3.41.	Safety	shell	Summary of Changes in NCEP Lipid Baseline Category to Maximum Post-Baseline Category	Exclude HDL	Up to Week 96
3.42.	Safety	shell	Summary of Changes in NCEP Lipid Baseline Category to Minimum Post-Baseline Category	For HDL only	Up to Week 96

Biomarkers					
3.43.	Safety	shell	Summary of Change from Baseline in Bone Biomarkers		All
3.44.	Safety	shell	Summary of Percentage Change from Baseline in Bone Biomarkers		Up to Week 96
3.45.	Safety	shell	Summary of Change from Baseline in Bone Biomarkers by Subgroup	See subgroups in Section 10.11	Up to Week 96
3.46.	Safety	shell	Table 3.461 Summary of Change from Baseline in Renal Biomarkers Table 3.462 Summary of Change from Baseline in Renal Biomarkers - Loge Transformed Data	Table 3.462 - report only up to Week 96	All
3.47.	Safety	shell	Summary of Percentage Change from Baseline in renal biomarkers		Up to Week 96
3.48.	Safety	shell	Table 3.481 Summary of Change from Baseline in Renal Biomarkers by Subgroup Table 3.482 Summary of Change from Baseline in Renal Biomarkers by Subgroup - Loge Transformed Data	Only Serum Cystatin C, eGFR (based on CKD-EPI-creatinine and CKD-EPI-cystatin C), Urine Beta-2 Microglobulin/Urine Creatinine ratio and Urine Retinol Binding Protein/Urine Creatinine ratio by baseline plasma HIV-1 RNA, baseline CD4+ cell count, Age (<50, vs ≥50) and presence of hypertension subgroups after week 48 will be analysed.	Up to Week 96
3.49.	Safety	shell	Statistical Analysis of Change from Baseline in Bone Biomarkers at Week X- (Multiple imputed Dataset - MAR)		Week 24, 48
3.50.	Safety	shell	Statistical Analysis of Change from Baseline in Bone Biomarkers at Week X by Subgroup – Observed Case	See subgroups in Section 10.11	Up to Week 96

3.51.	Safety	shell	Table 3.511 Statistical Analysis of Change from Baseline in Bone Biomarkers – MMRM Table 3.512 Statistical Analysis of Change from Baseline in Bone Biomarkers – Loge Transformed Data - MMRM		All
3.52.	Safety	shell	Table 3.521 Statistical Analysis of Change from Baseline in Renal Biomarkers at Week x - (Multiple imputed Dataset - MAR) Table 3.522 Statistical Analysis of Change from Baseline in Renal Biomarkers at Week x - Loge Transformed Data - (Multiple Imputed Dataset - MAR)		Week 24, 48
3.53.	Safety	shell	Table 3.531 Statistical Analysis of Change from Baseline in Renal Biomarkers at Week x by Subgroup - Observed Case Table 3.532 Statistical Analysis of Change from Baseline in Renal Biomarkers at Week x by Subgroup - Observed Case - Loge Transformed Data	Only Serum Cystatin C, eGFR (based on CKD-EPI-creatinine and CKD-EPI-cystatin C), Urine Beta-2 Microglobulin/Urine Creatinine ratio and Urine Retinol Binding Protein/Urine Creatinine ratio by baseline plasma HIV-1 RNA, baseline CD4+ cell count, Age (<50, vs ≥50) and presence of hypertension subgroups after week 48 will be analysed.	Up to Week 96
3.54.	Safety	shell	Table 3.541 Statistical Analysis of Change from Baseline in Renal Biomarkers – MMRM Table 3.542 Statistical Analysis of Change from Baseline in Renal Biomarkers - Loge Transformed Data - MMRM	For table 3.542, include all renal biomarkers. so parameters that in T3.541 also should be added	All

Treatment Emergent Laboratory Toxicities					
3.55.	Safety	shell	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities		All
3.56.	Safety	shell	Summary of Maximum Post-Baseline Emergent Hematology Toxicities	Where criteria is complex, i.e. AST>=2xULN and BLT >=2xULN use the whole condition	All
Other					
3.57.	Safety	Dori	Summary of Subjects Meeting Hepatobiliary Abnormality Criteria Post-Baseline Emergent Abnormalities	Footnote: Note: For ALT >=3xULN - <5xULN, >=5xULN - <10xULN, >=10xULN - <20xULN, >=20xULN, subjects were summarized based on post-baseline maximum emergent ALT.	All
3.58.	Safety	shell	Summary of True Positive Suicidal Indication/ Behaviour Alerts based on eCSSRS by Visit		All
3.59.	Safety	shell	Summary of Subjects with C-SSRS Suicidal Ideation or Behaviour at Baseline		All
3.60.	Safety	shell	Summary of Subjects with Post-Baseline C-SSRS Suicidal Ideation or Behaviour	Shell differs from Dori	All
3.61.	Safety	shell	Summary of Characteristics of Anxiety Adverse Events of Special Interest		All
3.62.	Safety	shell	Summary of Characteristics of Depression Adverse Events of Special Interest		All
3.63.	Safety	shell	Summary of Characteristics of Suicidality and Self Injury Adverse Events of Special Interest		All

3.64.	Safety	shell	Summary of Onset and Duration of the First Occurrence of Anxiety Adverse Events of Special Interest		All
3.65.	Safety	shell	Summary of Onset and Duration of the First Occurrence of Depression Adverse Events of Special Interest		All
3.66.	Safety	shell	Summary of Onset and Duration of the First Occurrence of Suicidality and Self Injury Adverse Events of Special Interest		All
3.67.	Safety	shell	Summary of Total Duration of Anxiety Adverse Events of Special Interest		Up to Week 96
3.68.	Safety	shell	Summary of Total Duration of Depression Adverse Events of Special Interest		Up to Week 96
3.69.	Safety	shell	Summary of Total Duration of Suicidality and Self Injury Adverse Events of Special Interest		Up to Week 96
3.70.	Safety	shell	Summary of Post Baseline Depression, Anxiety and Suicidal and Self-Injury Adverse Events by AE of Special Interest, Maximum DAIDS Toxicity Grade, and Prior History of Depression and Anxiety		All
3.71.	Safety	Dori	Summary of AST, ALT and Total Bilirubin Maximum Post-Baseline Emergent Toxicity By Baseline Hepatitis C Status		All
3.72.	Safety	shell	Summary of Change from Baseline in Fasting Lipids by subgroup – Lipid LOCF	Only Age (<50, vs ≥50) subgroup after week 48 will be analysed.	Up to Week 96
3.73.	Safety	shell	Statistical analysis of Change from Baseline in Fasting Lipids at Week X by subgroup – Lipid LOCF	Only Age (<50, vs ≥50) subgroup after week 48 will be analysed.	Up to Week 96
3.74.	Safety	Shell	Summary of Change from Baseline in Inflammation Biomarkers by Visit		Week 96,144
3.75.	Safety	Shell	Summary of Change from Baseline in telomere length at by Visit		EOS
3.76.	Safety	AE1	Summary of Drug-Related Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		All
3.77.	Safety	shell	Summary of Changes in NCEP Lipid Baseline Category to Week X		All
3.78.	Safety	AE3	Summary of Drug-Related Grade 2-5 Adverse Events		All

3.79.	Safety	AE5A	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Maximum Grade		All
3.80.	Safety	shell	Summary of Changes in Total Cholesterol/ HDL Ratio Baseline Category to Week x		All
3.81.	Safety	Table 3.57	Summary of Subjects Meeting Hepatobiliary Abnormality Criteria - All Post-Baseline Abnormalities	Same as Table 3.57 with the emergent criteria removed	Week 48, 96
3.89.	Safety	Table 3.55	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities - with GFR Toxicity Grading Re-Derived	Same as Table 3.55	Week 24
3.90.	Safety	Table 2.1 mid208959/ present_2018_01	Summary of Absolute Values of Fasting Lipids by Visit		Week 48 (ad hoc), 96, 144
3.91.	Safety	T3.33	Summary of Weight (kg) by Visit		Week 96
3.92.	Safety	T3.33	Summary of Change from Baseline in Weight (kg) by Visit		Week 96, 144
3.93.	Safety	T3.33	Summary of BMI (kg/m2) by Visit		Week 96
3.94.	Safety	T3.33	Summary of Change from Baseline in BMI (kg/m2) by Visit		Week 96, 144
3.95.	Safety	AE3	Summary of Common (>=2%) Drug-Related Adverse Events by Overall Frequency		Week 96, 144
3.96.	Safety	AE3	Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency	Plain Language Summary (PLS) requirements	Week 144
3.97.	Safety	EX1	Summary of Extent of Exposure to Investigational Product During Double Blind and Open Label Phase		Week 144
3.100.	Safety	mid208959/postcsr_2019_02/drivers/t_relrisk_g1.sas	Summary of Adverse Event Categories and Relative Risk		Week 144

10.17.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
3.1.	Safety	AE10	Plot of Common Adverse Events and Relative Risk	CS CORE	All
Laboratory Values Over Time					
3.2.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT	CS CORE	Up to Week 96
3.3.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	CS CORE	All
3.4.	Safety	shell	Bar Chart of Triglycerides, LDL Cholesterol and Total Cholesterol NCEP Categories at Week X vs. Baseline.		All
3.5.	Safety	shell	Bar Chart of Triglycerides, LDL Cholesterol and Total Cholesterol NCEP Categories at Baseline vs. Maximum Post-Baseline	Exclude HDL	Up to Week 96
3.6.	Safety	shell	Figure 3.61 Line Plot of Adjusted Mean (95% CI) Change From Baseline in Renal Biomarkers over Time — MMRM Figure 3.62 Line Plot of Ratio of Geometric Means (95% CI) in Renal Biomarkers over Time - LogeTransformed Data - MMRM	Two figures as 3.61 and 3.62	All
3.7.	Safety	shell	Line Plot of Adjusted Mean (95% CI) of Change from Basline in Bone Biomarkers over Time — MMRM		All
3.8.	Safety	shell	Bar Chart of HDL Cholesterol NCEP Categories at Baseline vs. Minimum Post-Baseline	For HDL only	Up to Week 96
3.9.	Safety	shell	Bar Chart of Total Cholesterol/ HDL Ratio Category at Week X vs. Baseline		All

3.10.	Safety	shell	Bar Chart of Total Cholesterol/ HDL Ratio Category at Baseline vs. Maximum Post Baseline		Up to Week 96
3.11.	Safety	shell	Bar Chart of HDL Cholesterol NCEP Categories at Week x vs. Baseline		All
3.12.	Safety	AE10	Plot of Common (>=2%) Grade 2-5 Adverse Events and Relative Risk		Week 96, 144
3.13.	Safety	AE10	Plot of Common (>=2%) Drug-Related Adverse Events and Relative Risk	use cut-off of >=2%	Week 96, 144
3.14.	Safety	Shell	Plot of Adverse Events Categories and Relative Risk		Week 96, 144

10.17.9. Virology tables

Virology: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	Viral Genotypic	shell	Summary of Subject Accountability: Genotypes Available at or prior to Week X		All
4.2.	Viral Phenotypic	shell	Summary of Subject Accountability: Phenotypes Available at or prior to Week X		All
4.3.	Viral Genotypic	shell	Summary of INSTI Mutations for Subjects Meeting CVW Criteria at or prior to Week X		All
4.4.	Viral Genotypic	shell	Summary of Major Mutations of NRTI, NNRTI and PI Classes for Subjects Meeting CVW Criteria at or prior to Week X		All
4.5.	Viral Genotypic	shell	Summary of Treatment Emergent INSTI Mutations at Time of CVW at or prior to Week X		All
4.6.	Viral Genotypic	shell	Summary of Changes in Major Mutations of NRTI, NNRTI and PI Classes from Baseline at Time of CVW for Subjects with CVW at or prior to Week X		All
4.7.	Viral Genotypic	shell	Summary of S-GSS at Time of CVW by Genotypic Cut-Off for DTG, 3TC, TDF and FTC at or prior to week X		All
4.8.	Viral Phenotypic	shell	Summary of Phenotype at Time of CVW by Phenotypic Cut-off at or prior to Week X		All
4.9.	Viral Phenotypic	shell	Number of Drugs to Which Subjects are Phenotypically Resistant at Time of CVW at or prior to Week X		All
4.10.	Viral Phenotypic	shell	Summary of Fold Change to DTG, 3TC, TDF and FTC at Time of CVW at or prior to Week X		All

10.17.10. Health Outcomes Tables

Health Outcomes: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
EQ-5D-5L					
5.1.	ITT(E)	shell	Summary of EQ-5D Category Scores by Visit – LOCF		All
5.2.	ITT(E)	shell	Summary of EQ-5D Utility and Thermometer Scores by visit - LOCF		All
5.3.	ITT(E)	shell	Summary of Change from Baseline in EQ-5D Utility and Thermometer Scores - LOCF		All
5.4.	ITT(E)	shell	Statistical Analysis of Change from Baseline in EQ-5D Utility Scores – MMRM - LOCF		All
5.5.	ITT(E)	shell	Statistical analysis of Change from Baseline in EQ-5D Thermometer Scores – MMRM - LOCF		All

10.17.11. Health Outcomes Figures

Health Outcomes: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
EQ-5D-5L					
5.1.	ITT(E)	shell	Line Plot of Adjusted Mean (95% CI) Change from Baseline in EQ-5D-5L Utility Score Over Time – MMRM - LOCF		All
5.2.	ITT(E)	shell	Line Plot of Adjusted Mean (95% CI) Change From Baseline in EQ-5D Thermometer Score Over Time – MMRM - LOCF		All

10.17.12. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population					
1.	ITT	Futility listing 1	Listing of Randomized and Actual Strata and Treatment Assignment	use screening value for actual strata	All
2.	ITT	Shell	Listing of Subjects Randomized But Not Treated	CS CORE (related to 'Listing for exclusion from any population)	All
3.	All Subjects Screened	ES7	Listing of Reasons for Screen Failure	CS CORE; add subreason, i.e # of IE criteria	All
4.	ITT(E)	BL1	Listing of Subjects for whom the Treatment Blind was Broken		
5.	ITT(E)	ES2	Listing of Reasons for Study Withdrawal	CS CORE	All
6.	ITT(E)	DV2	Listing of Important Protocol Deviations	CS CORE	All
7.	ITT(E)	Shell	Listing of Protocol Deviations Leading to Exclusion from the Per-Protocol Population	CS CORE	All
8.	ITT(E)	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	CS CORE	All
9.	ITT(E)	DM2	Listing of Demographic Characteristics	CS CORE	All
10.	ITT(E)	shell	Listing of subgroups		All
11.	ITT(E)	DM9	Listing of Race	CS CORE	All

Efficacy					
12.	ITT(E)	Shell	Listing of Quantitative and Qualitative Plasma HIV-1 RNA Data	Include the interpretation of whether the virus is detected or not ('Detected' or 'Not Detected') by the assay	All
13.	ITT(E)	Shell	Listing of Study Outcome (<50 c/mL) at Week X – Snapshot Analysis		All
Safety					
14.	Safety	HIV_IP5/ EX3	Listing of Investigational Product Exposure Data	CS CORE	All
15.	Safety	AE8	Listing of All Adverse Events	CS CORE	All
16.	Safety	AE8	Listing of Drug-Related Adverse Events		All
17.	Safety	AE8	Listing of Fatal Adverse Events	CS CORE	All
18.	Safety	AE8	Listing of Drug-Related Fatal Adverse Events		All
19.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	CS CORE	All
20.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product	CS CORE	All
21.	Safety	PSRAE1	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1-Section 2)		All
22.	Safety	PSRAE3	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)		All
23.	Safety	PSRAE4	Listing of Possible Suicidality-Related Adverse Event Data (Section 4)		All
24.	Safety	PSRAE5	Listing of Possible Suicidality-Related Adverse Event Data (Section 5-Section 8)		All
25.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	CS CORE	All
26.	Safety	AE2	Listing of Relationship of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	CS CORE	All
27.	Safety	LB5	Listing of Clinical Chemistry Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern	CS CORE	All
28.	Safety	LB5	Listing of Hematology Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern	CS CORE	All
29.	Safety	UR2a	Listing of Urinalysis Data for Subjects with Abnormalities of Potential Clinical Concern	CS CORE, use all data; if data is form both dipstick and concentration, display separately	All

10.17.13. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population					
30.	All Subjects Screened	Shell	Listing of Subject Recruitment by Country and Site Number		All
31.	All Subjects Screened	ES9	Listing of Subjects Who Were Rescreened		All
32.	ITT(E)	Shell	Listing of Visit Dates		All
33.	All Subjects Screened	Shell	Listing of Study Populations		All
34.	Safety	Shell	Listing of DTG Pharmacokinetic Concentration Data at Liver Event	Please this listing under 'Safety, Listing – Other' section.	from week 48
35.	ITT(E)	Shell	Listing of Hepatitis Test Results		All
36.	ITT(E)	CDC3	Listing of CDC Classification of HIV Infection at Baseline		All
37.	ITT(E)	RF2	Listing of HIV Risk Factors		All
38.	ITT(E)	Shell	Listing of Screening Cardiovascular Risk Assessment Data		All
39.	ITT(E)	MH2	Listing of Current and Past Medical Conditions at Baseline		All
40.	ITT(E)	MH2	Listing of Current and Past Medical Conditions at Baseline – subjects at sites in Mexico only		EOS
41.	ITT(E)	Shell	Listing of History of Cardiac Therapeutic Procedures		All
42.	ITT(E)	Shell	Listing of Investigational Product Accountability		All
43.	ITT(E)	CM2	Listing of Concomitant Medications	CS CORE	All
44.	ITT(E)	CM2	Listing of Concomitant Medications – subjects at sites in Mexico		EOS
45.	ITT(E)	CM6	Listing of Relationship Between ATC Level 1, Ingredient and Verbatim Text		All
46.	ITT(E)	CM2	Listing of Prior ART Medications		All
47.	ITT(E)	CM2	Listing of Concomitant ART Medications		All

48.	ITT(E)	CM2	Listing of Concomitant ART Medications– subjects at sites in Mexico only		EOS
49.	ITT(E)	CM6	Listing of Relationship Between ATC Level 4, Ingredient and Verbatim Text		All
Efficacy					
50.	ITT(E)	shell	Listing of Plasma HIV-1 RNA data for subjects with Confirmed Virologic Withdrawal		All
51.	ITT(E)	shell	Listing of CD4+ Cell Count Data		All
52.	ITT(E)	HIV4	Listing of Stage 3 HIV-1 Associated Conditions	List only stage 3 associated conditions	All
53.	ITT(E)	shell	Listing of subjects Efficacy related discontinuation = Failure (ERDF)		All
54.	ITT(E)	shell	Listing of subjects Treatment related discontinuation = Failure (TRDF)		All
55.	ITT(E)	shell	Listing of Subjects who Reached Week 48 prior to and after the Week 24 unblinding – Bias Sensitivity Analysis		48
Safety					
56.	Safety	HIV_IP5	Listing of Investigational Product Exposure Data – subjects at sites in Mexico	CS CORE	EOS
57.	Safety	AE8	Listing of Non-Serious AEs for subjects at sites in Mexico		EOS
58.	Safety	AE8	Listing of SAEs for subjects at sites in Mexico		EOS
59.	Safety	AE8	Listing of SAEs for subjects at sites in Mexico		EOS
60.	Safety	shell	Listing of Cardiovascular Events		All
61.	Safety	CP_EG5 / CP_EG4 Or dori	Listing of All ECG Findings for Subjects with an Abnormal Finding		All
62.	Safety	VS4	Listing of Vital Signs	Please include all visits available.	All
63.	Safety	shell	Listing of Post Baseline Maximum ALT and Maximum Bilirubin		All
64.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		All
65.	Safety	LIVER6	Listing of Liver Event Information for RUCAM Score		All
66.	Safety	LIVER7	Listing of Liver Biopsy Details		All
67.	Safety	LIVER8	Listing of Liver Imaging Details		All
68.	Safety	MH2	Listing of Past and Current Liver Disease Medical Conditions		All

69.	Safety	shell	Listing of Laboratory Data from Liver Event Follow-Up		All
70.	Safety	Dori	Subjects Meeting Hepatobiliary Abnormality Criteria - Post-Baseline Emergent Abnormalities	This is about "emergent" – the subjects do not have such conditions at baseline. If missing baseline (i.e. some or all ALT, BILT etc were missing), we assume they are normal. Any conditions met post-baseline will be included in the table.	All
71.	Safety	shell	Listing of C-SSRS Suicidal Ideation and Behaviour Positive Alerts (4-9)		All
72.	Safety	shell	Listing of C-SSRS Suicidal Ideation and Behaviour Data	Similar shell for listing 71	All
73.	Safety	shell	Listing of C-SSRS False Positive Alerts with Corresponding Reasons		All
74.	Safety	shell	Listing of all C-SSRS True Positives, with Corresponding Reasons for not being considered an AE or SAE		All
75.	Safety	PREG1a	Listing of Subjects Who Became Pregnant During the Study		All
76.	Safety	shell	Patient profiles for subjects meeting protocol defined liver stopping criteria		All
77.	Safety	shell	Patient profiles for subjects meeting confirmed virologic withdrawal criteria		All
78.	Safety	Dori	Listing of Liver Event Results and Time of Event Relative to Treatment		All
Virology					
79.	ITT(E)	shell	Listing of All Genotypic Data		All
80.	Viral Genotypic	shell	Listing of Treatment Emergent Genotypic Mutations		All
81.	Viral Genotypic	shell	Listing of Genotype by Genotypic Cut-Off - CVWs		All
82.	ITT(E)	shell	Listing of All Phenotypic Data		All
84.	Viral Phenotypic	shell	Listing of Net Assessment Score - CVWs		All

85.	ITT(E)	shell	Listing of Genotypic and Phenotypic Data for Subjects with Confirmed Virologic Withdrawal Criteria		All
86.	ITT(E)	shell	Listing of Genotypic and Phenotypic Data for Subjects with on-treatment Virology Results at non-CVW timepoints		All
87.	ITT(E)	shell	Listing Subject Level Summary of Key Virologic Data for Subjects with Confirmed Virologic Withdrawal or On-Treatment Non-CVW Timepoints		All
Health Outcomes					
88.	ITT(E)	shell	Listing of EQ-5D Category, Utility and Thermometer Scores		All

Other					
90.	Safety	shell	Listing of Renal Biomarker Data		All
91.	Safety	shell	Listing of Bone Biomarker Data		All
92.	Safety	shell	Listing of Inflammation Biomarkers data		Week 96,144
93.	Safety	shell	Listing of Telomere Length Data		EOS
94.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	Keep in ICH listing in HARP	All
95.	Safety	AE8	Listing of Drug-related Non Fatal Serious Adverse Events	Keep in ICH listing in HARP	All
96.	Safety	Listing 70	Subjects Meeting Hepatobiliary Abnormality Criteria - All Post-Baseline Abnormalities	Same as Listing 70 with the emergent criteria removed	Week 48, 96
97.	Safety	LB5	Listing of Clinical Chemistry Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern - with GFR Toxicity Grading Re-Derived	Keep in ICH listing in HARP CS CORE	Week 24
98.	Safety	CVATIA1	Patient Profiles for Subjects with Cardiovascular Events	Provided if detailed cardiovascular event information is available.	Week 144

10.18. Appendix 18: Example Mock Shells for Data Displays

Mock shells are included in a separate document.

There are no new mock shells added for EOS, therefore, no update is needed for the previous mock shell document.