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

Title	:	Reporting and Analysis Plan for A Phase III, randomised, multicenter, parallel-group, non- inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus lamivudine in HIV 1 infected adults who are virologically suppressed
Compound Number	:	GSK1349572 + GR109714 (GSK3515864)
Effective Date	:	19-DEC-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Reports for Protocol 204862.
- This RAP will be provided to the study team members to convey the content of the 204862 Statistical Analysis Complete (SAC) deliverables for the reporting effort up to Week 144. An addendum to this RAP will be developed at a later stage to convey the content of the Late Switch Phase and End of Study SAC deliverables.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There are no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 5 (Dated: 07/DEC/2017).

2.2. Study Objective(s) and Endpoint(s)

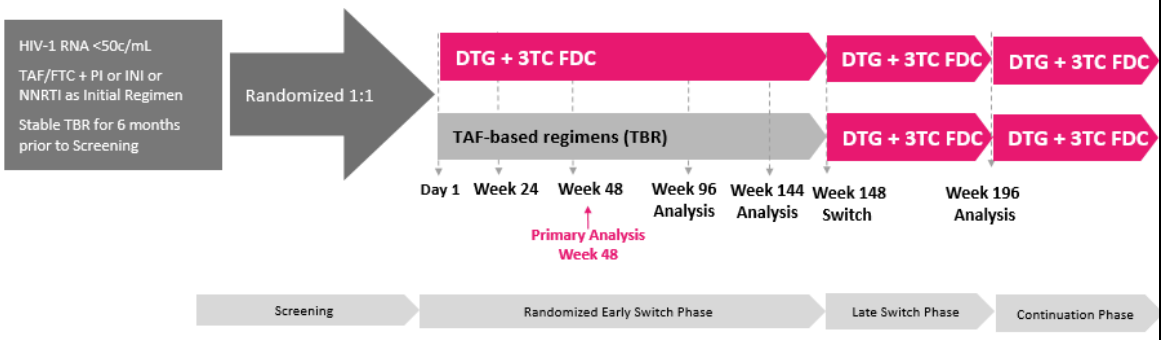
Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of Tenofovir alafenamide (TAF) based regimen (TBR) over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure (subjects with plasma HIV-1 RNA ≥50 copies c/mL) endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24, 96 and 144 weeks	• Subjects with plasma HIV 1 RNA ≥50 copies c/mL endpoint as per FDA snapshot category at Weeks 24, 96 and 144 • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR over 24, 48, 96 and 144 weeks	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell count ratio at Weeks 24, 48, 96 and 144 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48, 96 and 144

Objective	Endpoint
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through 144 weeks • Proportion of subjects who discontinue treatment due to AEs through 144 weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24,48, 96 and 144
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24,48, 96 and 144
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24, 48, 96 and 144 (or Withdrawal from the study)
Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with plasma HIV-1 RNA <50c/mL using the Snapshot algorithm at Weeks 24, 48, 96 and 144 • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
To asses willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48, 96 and 144
To evaluate inflammation biomarkers and insulin resistance in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 48, 96 and 144
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 196 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 196 • Incidence and severity of AEs and

Objective	Endpoint
	laboratory abnormalities over 196 weeks • Proportion of subjects who discontinue treatment due to AEs over 196 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 196 • Change from Baseline in renal and bone biomarkers at Week 196 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at Week 196
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 196 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 196 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 196 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at Week 196
To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients	Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4.
To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients	Population estimates of DTG and 3TC PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a 200-week, Phase III, randomised, open-label, active-controlled, multicenter, parallel-group non-inferiority study. The study will include a Screening Phase (up to 28 days), a Randomised Early Switch Phase (Day 1 up to Week 148), a Randomised Late Switch Phase (Week 148 up to Week 200200200), and a Continuation Phase (post Week 200).
Dosing	• Patients receiving DTG + 3TC will receive DTG (50mg) + 3TC (300mg) once daily. Patients receiving TBR will receive the dose as determined by their prescribing physician.
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• Approximately 550 subjects will be randomised 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 196 weeks, or to continue their TBR for 148 weeks, and then switch to DTG + 3TC up to Week 196 (if HIV1 RNA <50 c/mL at Week 144 (or at Week 148 if re-tested))
Interim Analysis	• One analysis will be conducted to evaluate the primary objective of the protocol when all subjects have completed their Week 48 visit and any HIV-1 RNA re-tests as appropriate. An interim analysis will be conducted when all subjects have completed their Week 24 visit and any Weeks HIV-1 RNA re-tests as appropriate (see Blinding Agreement for more details). To minimise bias, the Week 24 results will not be shared with subjects and investigators, or presented externally until after the last subject completes their Week 48 visit

See study protocol for further details

2.4. Statistical Hypotheses / Statistical Analyses

This study is designed to show that the antiviral effect of switching to a simplified two-drug regimen of DTG + 3TC once-daily is not inferior to continuation of their TBR at week 48 in HIV-1 infected ART-experienced subjects. Assuming a true 2% virologic failure rate in each arm, a non-inferiority margin of 4%, and a 2.5% one-sided

significance level, this study requires 275 subjects per treatment arm. This would provide 92% power to show non-inferiority for the proportion of subjects with virologic failure according to the FDA snapshot algorithm at 48 weeks post-switch.

While the targeted study size was 550 randomised subjects (from a target of 800 screened subjects), the study was over-enrolled based on an unexpected surge in recruitment in the last week of screening ending with a final number of 743 subjects randomised. This will provide 97.3% power to show non-inferiority with the current assumptions, and non-inferiority can be declared if the actual observed treatment difference in the trial is less than or equal to 1.6%.

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

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

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim analysis will be performed at Week 24. To minimise bias, the results of the Week 24 results will not be shared with subjects and investigators, or presented externally until after the last subject completes their Week 48 visitPlease refer to the Blinding Agreement for more details.

The planned analysis at Week 24 will be performed after the completion of the following sequential steps:

- Last subject has completed their visit at Week 24 as defined in the protocol, including any re-test if required.
- All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
- All criteria for unblinding[1] the randomisation codes at Week 24 have been met.

No adjustment for multiplicity will be made as the Week 24 analyses will be secondary, however non-inferiority at Week 24 will be declared if the upper bound of a two-sided 95% confidence interval for the difference in virologic failure rates between the two treatment arms is less than 4%[2].

An IDMC was instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of the study. An ad-hoc review of data by the IDMC will be triggered whenever the number of confirmed virologic withdrawals (CVWs) exceeds thresholds pre-specified in the IDMC charter. Full details of the methods, timing, decision criteria and operating characteristics are pre-specified in the IDMC Charter. Details of the analyses and outputs provided to the IDMC are detailed in an IDMC RAP.

3.2. Final Analyses

The primary analysis is at Week 48. Additional analyses will be performed at Weeks 96, 144 and 196 and at the end of the continuation phase. Analyses performed after Week 48 are considered interim analyses beyond the primary analysis.

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[1] Although this is considered an open-label study, any data transfers/dry-runs prior to formal analyses will be based on blinded or dummy treatment allocation. Any references to unblinding the study in this analysis plan pertains to the process of unmasking the actual randomisation codes at formal data base locks.

[2] Please refer to Section 7.1.4 for details and conditions for presentation of test for superiority.

The planned analyses at Weeks 48, 96, 144 and 196 and end of continuation phase[3] will be performed after the completion of the following sequential steps:

- Last subject has completed their relevant visit at week 48 (96, 144, 196 or end of continuation) as defined in the protocol, including any re-test if required.
- All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
- All criteria for unblinding the randomisation codes at Week 48 have been met.

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

The Late Switch Phase and End of Study analysis will be covered by a RAP addendum.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All subjects screened	• Comprises all subjects screened for inclusion in the study, including screen-failures. • This population will be based on the treatment to which the subject was randomised. Screen-failures will be categorised as "Non-randomised".	• Study Population
Randomised	• The Randomised population will consist of all subjects who are randomised in the study	• Study Population
Intent-to-Treat (ITT)	• Comprises all randomised subjects • Subjects will be assessed according to the treatment to which the subject was randomised regardless of treatment actually received. • Any subject receiving a treatment randomisation number will be considered to be randomised.	• Efficacy (sensitivity analyses)
Intent-To-Treat Exposed (ITT-E)	• Comprises all randomised subjects who receive at least one dose of study treatment either DTG + 3TC or TBR.	• Efficacy and Health Outcomes

[3] Note that analyses for time points will be performed when subjects complete visits relevant to that time point i.e. Week 48 analysis takes place when the last patient has completed their Week 48 visit, and not when they have completed their Week 48, Week 96, Week 144, Week 196 and end of continuation phase.

Population	Definition / Criteria	Analyses Evaluated
	• This population will be based on the treatment to which the subject was randomised. • Any subject who receives a treatment randomisation number will be considered to have been randomised.	
Per-Protocol (PP)	• This population will consist of subjects in the ITT-E Population with the exception of significant protocol violators. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Section 13.1 (Protocol Deviation Management and Definition for Per-Protocol Population).	• Efficacy (Sensitivity Analysis)
CVW	• Comprises all subjects in the ITT-E population who have met the derived CVW criteria	• Genotypic • Phenotypic • Efficacy
potential Precautionary Virologic Withdrawal (pPVW)	• Comprises subjects in the ITT-E population having 2 consecutive measurements between 50 and 200 c/mL	• Genotypic • Phenotypic
Safety	• Comprises all subjects who receive at least one dose of study treatment either DTG + 3TC or TBR. • This population will be based on the treatment the subject actually received[4].	• Safety
Sparse Pharmacokinetic Population	• All subjects who received at least 1 dose of DTG/3TC FDC and have evaluable sparse samples with drug concentrations reported, where samples are collected according to the sparse sampling schedule (through Week 48).	• PK

[4] As recorded on IVRS. If the randomised treatment is incorrect, the actual treatment will only be recorded in IVRS through sponsor intervention.

Population	Definition / Criteria	Analyses Evaluated
Intensive Pharmacokinetic Concentration Population	• The subset of subjects enrolled into intensive PK sampling, who received at least 1 dose of DTG/3TC FDC and have evaluable drug concentrations reported, where samples are collected according to the intensive sampling schedule (Week 4 only).	• PK
Intensive Pharmacokinetic Parameter Population	• All subjects in the Intensive Pharmacokinetic Concentration Population who provide at least one evaluable PK parameter.	• PK

NOTES :

- Please refer to Appendix 14: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Term	Definition
Study Deviation Rules Document	The document describing study deviations (and associated coding/naming conventions) that may be identified during a study and the frequency of study deviation reviews.
Protocol Deviation (PD)	Any departure from study-specific requirements specified in a protocol. Subsets of protocol deviations are categorized as important or significant.
Important Protocol Deviations	A subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. All important deviations have a Violation Flag in CTMS and are associated with a Rule Number.
Significant Protocol Deviations	Considered a subset of important protocol deviations, typically impacting efficacy assessments, which lead to the exclusion from the per-protocol population. All significant deviations are captured in CTMS and are associated with a Rule Number.

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 analysis population (Significant deviations) will also be summarised and listed (see Section 13.1).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [20-Jul-2018, version 2.0].

- Data will be reviewed prior to unblinding and freezing of the database with the aim of capturing and categorising all important deviations and deviations which may lead to exclusion from the analysis in the protocol deviations SDTM dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Subgroup Display Descriptors

Treatment Group Description	Order [1]
DTG + 3TC	1
TBR	2

NOTES:

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

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. DTG + 3TC vs TBR

5.2. Baseline Definitions

For all endpoints (unless otherwise stated) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data are missing no derivation will be performed and baseline will be set to missing.

Unless otherwise specified, the baseline definitions specified in the table below will be used for derivations for endpoints/parameters and indicated on summaries and listings.

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

5.3. Multicentre Studies

Data will be summarised for all centres combined. Country will be treated as an exploratory subgroup for analyses of the primary efficacy endpoint.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

- The following is a list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses
- Additional covariates of clinical interest may also be considered.

Category	Details
Randomisation Strata	Randomisation is stratified by baseline third agent class: • Baseline third agent class (PI, NNRTI, INI). For analysis purposes, randomisation strata will be derived using eCRF data, even if this differs from the strata captured in IVRS (details of how this is derived can be found in Section 13.6.11) All statistical analyses will adjust for the above randomisation strata, unless stated otherwise. Treatment-by-Strata interactions will be assessed as specified in the analysis sections.
Covariates	• Age (years): <35, 35 to <50, ≥50 (or continuous) • Gender: Male & Female • Baseline CD4+ cell count: ○ <200, 200 to <350, ≥350 cells/mm^3 (or continuous) • Race (White, Black or African American, Asian, Other), or (White, Non-White) • BMI (<vs. ≥ 25 kg/m^2) (or continuous) • Smoking status (Never vs. Former vs. Current Smoker), • Vitamin D use (Yes vs. No) • Diabetes mellitus (Yes vs. No) • Hypertension (Yes vs. No) • HCV-coinfection (Yes vs. No)

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups 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.

If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Subgroups
Randomisation Strata	Randomisation is stratified by baseline third agent class: • Baseline third agent class (PI, NNRTI, INI). For analysis purposes, randomisation strata will be derived using eCRF data, even if this differs from the strata captured in IVRS All statistical analyses will adjust for the above randomisation strata, unless stated otherwise. Treatment-by-Strata interactions will be assessed as specified in the analysis sections.
Demographic and Baseline Characteristics	• Age (years): <35, 35 to <50, ≥50, and <50 vs. >=50 • An additional split of Age <50 and ≥60, or <60 and ≥60 may also be performed if specifically required for regulatory purposes) • Gender: Male & Female • Baseline CD4+ cell count: o <200, 200 to <350, ≥350 cells/mm^3 o <500, ≥500 cells/mm^3 • CDC HIV-1 classification • Country • Race: White, Black or African American, Asian, Other; and: White vs non-White

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

	Endpoint			
Subgroup	**Proportion of patients with plasma HIV-1 RNA <50[5] copies c/mL[6]**	**Summary of Study Snapshot outcomes (Plasma HIV-1 RNA >=/< 50 c/mL)**	**CD4+ Cell Count and CD4+/CD8+ Ratio Change from Baseline**	**AEs[7]**
Baseline third agent class (PI, NNRTI, INI)	Y	Y	Y	Y
Age (years): <35, 35 to <50, ≥50	Y	Y	Y	Y
Age (years): <50, ≥50	Y	Y		
Gender: Male & Female	Y	Y	Y	Y
Baseline CD4+ cell count: <200, 200 to <350, ≥350 cells/mm3 and <500, ≥500 cells/mm3	Y	Y	Y	Y
CDC HIV-1 classification: Stage 0-3	Y	Y	Y	Y
Country	Y	Y		
Race: White, Black or African American, Asian, Other	Y	Y	Y	Y
Race: White, non-white	Y	Y	Y	

5.5. Multiple Comparisons and Multiplicity

The primary comparison of interest is the comparison between DTG + 3TC and TBR for the primary endpoint in the ITT-E population. This analysis will be adjusted for by the

[5] A sensitivity analysis will also be performed for the following endpoint: HIV-1 RNA <40 c/mL and Target Not Detected Status. See Section 7.2.5 for more details.

[6] Includes forest plot for unadjusted difference of patients with plasma HIV 1 RNA <50 copies c/mL between treatment arms.

[7] Subgroup analyses will be presented for the following analyses: Adverse Events by System Organ Class, Maximum Toxicity; and Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study (see Section 13.14 Full Data Displays for more information)

actual stratification factor as determined from the eCRF data (not as recorded in IVRS) randomisation.

No adjustment for multiplicity is required as there is only one primary comparison of interest.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
13.1	Appendix 1: Protocol Deviation Management
13.2	Appendix 2: Schedule of Activities
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	Appendix 8: Values of Potential Clinical Importance
13.9	Appendix 9: Population Pharmacokinetic (PopPK) Analyses
13.10	Appendix 10: Time to Event Details
13.11	Appendix 11: Snapshot
13.12	Appendix 12: Abbreviations & Trade Marks
13.13	Appendix 13: Model Checking and Diagnostics for Statistical Analyses
13.14	Appendix 14: List of Data Displays
13.15	Appendix 15: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Table 1 provides an overview of the planned study population analyses, with full details of data displays being presented in 13.14: List of Data Displays.

Table 1 Overview of Planned Study Population Analyses

Display Type	Data Displays 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
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 and baseline characteristics		
Demographic Characteristics[5]	Y	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	Y
Distribution of CD4+ Cell Counts	Y	
History of Cardiac Therapeutic Procedures		Y
Medical Conditions, Concomitant Medications & Antiretroviral Therapy		
Medical Conditions (Current and Past)	Y	Y
Medical Conditions: Sub-conditions (Current/Past)	Y	
Concomitant Medications (non-ART)	Y[7]	Y[8]
Prior and Concomitant ART Medications	Y	Y[9]
Baseline third agent class (Strata) [10]	Y	Y

Display Type	Data Displays Generated	
	Table	Listing
Lipid Modifying agents (Baseline and Post-Baseline)	Y	
Other		
History of Depression and Anxiety at Baseline	Y	
Summary of Past and Current Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions	Y	
History of Cardiac Therapeutic Procedures		Y
Investigational Product Accountability		Y

NOTES:

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

1. ITT-E. One listing of subjects randomised but not treated, and one listing of planned and actual treatment strata.
2. ITT-E and All Subjects screened population.
3. Subject Accountability by Phase (Overall, Early Switch Phase, Late Switch Phase)
4. Subjects who have not been recorded as 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, BMI (kg/m^2) and child-bearing potential 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. Three separate tables, summarised by: 1) Ingredient ATC Level 1, 2) Ingredient combinations and 3) 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).)
8. One listing for concomitant non-ART medications and one listing showing the relationship between verbatim text, ingredient and ATC Level 1.
9. 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.
10. Based on the actual third agent class that subjects were classified into according to data captured on the eCRF.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analysis

7.1.1. Summary Measure

Proportion of subjects with plasma HIV-1 RNA ≥50 copies c/mL at Week 48 using the snapshot algorithm.

7.1.2. Population of Interest

The primary efficacy analyses will be based on the Intent-To-Treat Exposed (ITT-E) population unless otherwise specified.

7.1.3. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent events will be accounted for as per the FDA snapshot algorithm.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in 13.14: List of Data Displays and will be based on GSK data standards and statistical principles commonly applied in GSK HIV-1 trials.

Table 2 provides an overview of the planned efficacy analyses, with full details of data displays being presented in 13.14: List of Data Displays.

Table 2 Overview of Planned Primary Efficacy Analyses

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Proportion of Subjects with plasma HIV 1 RNA ≥50 copies c/mL at week 48 – Snapshot							
Primary Analysis	Y[1]		Y[4]		Y[3]		
Study Outcome [2] based on the Snapshot				Y			Y
Sparse Data Analysis	Y[5]						

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' and 'Intent-to-Treat' (sensitivity) populations.
[2] Study outcomes (i.e., virologic failure, virologic success (response below 50 c/mL) or no virologic data at Week X window) based on the snapshot algorithm.
[3] Line plots, with 95% confidence intervals, for the proportion of subjects with virologic failure by treatment group at each visit.
[4] Listing of Quantitative and Qualitative Plasma HIV-1 RNA Data based on the snapshot algorithm.

[5] See methodology section below for more information.

7.1.4.1. Statistical Methodology Specification

Endpoint

- Proportion of subjects with plasma HIV 1 RNA ≥50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
- 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. The nature of this missing data will be further classified in Snapshot summaries as either 'Virologic Failure' or 'No Virologic Data at Week 48'. Subjects who change their ART regimen prior to the visit of interest will be considered virologic failures since changes in ART are not permitted in this protocol (with the exception of a change in the booster ART as detailed below).
- 'Virologic failure' includes subjects who changed any ART; subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy, discontinued for other reason while not < 50 c/mL, and subjects who have HIV-1 RNA ≥ 50 c/mL at the visit of interest.
- Virologic success includes subjects who have HIV-1 RNA <50 c/mL at the visit of interest.
- The only protocol-permitted substitutions are as follows:
    - A switch from a PI boosted with RTV to the same PI boosted with cobicistat is allowed.
    - A switch from a PI boosted with cobicistat to the same PI boosted with RTV is allowed.

Virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is On-treatment within the visit of interest analysis window see Section 13.3. Full details of the Snapshot algorithm are in Section 13.11.

Model Specification

- The primary endpoint will be analysed using a stratified analysis with Cochran-Mantel-Haenszel (CMH) weights, adjusting for baseline third agent class (PI, NNRTI, INI).
- 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 three Baseline analysis strata:
    - Baseline third agent: PI
    - Baseline third agent: NNRTI
    - Baseline third agent: INI
- If n_k is the number of DTG + 3TC treated subjects, m_k is the number of PI-, NNRTI- or INI-based ART 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 virologic failure proportions between the two treatment arms, r_d-r_a, for the *k*th strata.

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

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

using the variance estimator, var(d_{cmh}), given by [Sato ,1989], which is consistent in both sparse data and large strata.

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

where

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

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

Model Checking & Diagnostics

- Not applicable

Model Results Presentation

- Adjusted CMH estimate of the difference in the proportion of virologic failure between each treatment group (DTG + 3TC – TBR) and corresponding 95% confidence interval.
- Non-inferiority will be concluded if the upper bound of the two-sided 95% confidence interval (CI) for the CMH adjusted difference in the proportion of patients with virologic failure in the DTG +3TC group minus the proportion of patients with virologic failure in the TBR group is less than 4%.
- If ITT-E and Per Protocol analyses show non-inferiority (see Sensitivity and Supportive Analyses section below), superiority will be declared if the upper end of the confidence interval for the CMH adjusted difference in the proportion of patients with virologic failure in the DTG +3TC group minus the proportion of patients with virologic failure in the TBR group is below 0% for the ITT-E population analysis. If superiority is declared the p-value for superiority will also be calculated and presented.
- Figures: Line plots, with 95% confidence intervals, for the proportion of subjects >= 50 c/mL as per the FDA snapshot by treatment group at each visit.

Subgroup Analyses

- Subgroup analyses will not be performed for this endpoint

Sensitivity and Supportive 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 TBR will be tested at the two-sided 5% level of significance.
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 randomised but not exposed to study treatment will be classified as non-responders.
3. A sensitivity analysis will be conducted to assess the impact of sparse data (Miettinen, 1985).
   - The estimate is computed from Miettinen-Nurminen (score) confidence limits for the stratum risk differences. The score confidence interval for the risk difference in stratum h can be expressed as $\hat{d}'_h \pm z_{\alpha/2} s'_h$, where $\hat{d}'_h$ is the midpoint of the score confidence interval and s'_h is the width of the confidence interval divided by $2z_{\alpha/2}$. The summary score estimate of the common risk difference is computed as:

$$\hat{d}_S = \sum_h \hat{d}'_h w'_h$$

where

$$w'_h = (1/s'^2_h) / \sum_i (1/s'^2_i)$$

The variance of $\hat{d}_S$ is computed as

$$\hat{\sigma}^2(\hat{d}_S) = 1 / \sum_h (1/s'^2_h)$$

The $100(1-\alpha)\%$ summary score confidence limits for the common risk difference are:

$$\hat{d}_S \pm \left(z_{\alpha/2} \times \hat{\sigma}(\hat{d}_S) \right).$$

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

- Patients with plasma HIV 1 RNA ≥50 copies c/mL at week 24, 96 and 144.
- Patients with plasma HIV 1 RNA <50 copies c/mL at weeks 24, 48, 96 and 144.
- CD4+ cell count at Weeks 24, 48, 96 and 144.
- CD4+/CD8+ cell count ratio at Weeks 24, 48, 96 and 144.
- Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48, 96 and 144.

7.2.2. Summary Measures

- Proportion of subjects with plasma HIV 1 RNA ≥50 copies c/mL at weeks 24, 96 and 144 using the snapshot algorithm.
- Proportion of subjects with plasma HIV 1 RNA <50 copies c/mL at weeks 24, 48, 96 and 144 using the snapshot algorithm.
- Change from baseline in CD4+ cell count at Weeks 24, 48, 96 and 144.
- Change from baseline in CD4+/CD8+ cell count ratio at Weeks 24, 48, 96 and 144.
- Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48, 96 and 144.

7.2.3. Populations of Interest

The secondary efficacy analyses will be based on the ITT-E population.

7.2.4. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent events will be accounted for as per the FDA snapshot algorithm for the analyses of secondary endpoints of plasma HIV 1 RNA <50 copies c/mL and plasma HIV 1 RNA ≥50 copies c/mL. Intercurrent events will not be controlled for in disease progression and CD4+ cell count analyses.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 14: List of Data Displays.

Table 3 provides an overview of the planned secondary efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Secondary 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														
Secondary analysis at Week X	Y		Y		Y									
Study Outcome based on the Snapshot at Weeks 24, 96 and 144				Y			Y							
By Visit				Y										
Proportion of subjects without virologic or virologic/tolerability failure at Week X[10]	Y	Y[11]					Y							
Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL – Snapshot														
Secondary analysis at Week X[6]	Y[12]													
Secondary analysis by Visit through Week X[6]				Y	Y									
Secondary analysis by subgroup at Week X[6]				Y	Y[1]									
Study Outcomes at Week X[6]				Y[12]										
Study Outcomes by subgroup at Week X[6]				Y										

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
Confirmed Virologic Withdrawal (CVW)														
CVW by Visit[12]	Y						Y							
HIV-1 RNA distribution at time of suspected and confirmed Virologic withdrawal	Y													
Potential Precautionary Virologic Withdrawal (pPVW)														
pPVW by Visit							Y							
Plasma HIV-1 RNA over time – Observed														
By Visit through Week X[6]						Y[2]	Y[2,9]				Y[5,12]			
CD4+ Cell Counts[3]														
By Visit through Week X[6]						Y[2]	Y				Y			Y
By Subgroup at Week X[6]											Y			
CD4+/CD8+ Cell Count Ratio[3]														
By Visit through Week X[6]						Y[2]	Y				Y			Y
Post-baseline HIV-1 Disease Progression[4]														
HIV Conditions including Recurrences at Week X[6,7,12]				Y			Y							
HIV Conditions excluding Recurrences at Week X[6,7,12]				Y										
HIV Disease Progressions at Week X[6,8,12]				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. Individual plasma HIV-1 RNA and CD4+ profiles only for subjects with at least one HIV-1 RNA levels ≥ 50 c/mL observed including at Day 1 and through withdrawal visit.
3. Using observed case (OC) data which contains the data that is available at a particular time point, with no imputation for missing values.
4. HIV disease progressions categories: CDC Category Stage 1 at enrolment to Stage 3 event; CDC Category Stage 2 at enrolment to Stage 3 event; CDC Category Stage 3 at enrolment to New Stage 3 Event; CDC Category Stage 1, 2 or 3 at enrolment to Death.
5. Descriptive summary of the log10 change from baseline HIV-1 RNA by visit presented.
6. Week X refers to Week 24, Week 48, Week 96 and week 144.
7. Stage 3 only.
8. Progression to Stage 3 or death.
9. Includes target detected/not detected flag see Section 13.6.3 for more information.
10. Outputs will be produced for Efficacy related discontinuation = Failure (ERDF) and Treatment related discontinuation = Failure (TRDF).
11. Kaplan-Meier Plot of Time to Failure – ERDF/TRDF.
12. Repeated on the following endpoints: <40 c/mL and <40 c/mL and Target Not Detected Status.

7.2.5.1. Statistical Methodology Specification

Endpoint
• Proportion of subjects with plasma HIV 1 RNA ≥50 copies c/mL at Weeks 24, 96 and 144, and plasma HIV 1 RNA <50 copies c/mL at Week 24, Week 48, Week 96 and Week 144 using the Snapshot algorithm for the ITT-E population. • The analysis approach will follow the methods as described for the primary endpoint.
Model Specification
• Specification will be same as described for the primary endpoint
Model Checking & Diagnostics
• Same as described for the primary endpoint
Model Results Presentation
• Model presentation will be the same as described for the primary endpoint. • Proportion subjects with plasma HIV 1 RNA ≥50 copies c/mL will be analysed at Weeks 24, 96 and 144. Proportion subjects with plasma HIV 1 RNA <50 copies c/mL will be analysed at Week 24, Week 48, Week 96 and Week 144 • For virologic success (plasma HIV-1 RNA <50 c/mL) endpoint, non-inferiority of switching to DTG + 3TC compared to continuation of TBR (as per FDA snapshot algorithm) will be assessed using a -8% non-inferiority margin. Non-inferiority will be concluded if the lower bound of a 2-sided 95% confidence interval for the difference in success rates between the two treatment arms is greater than -8%. Figures: Line plots, with 95% confidence intervals.
Subgroup Analyses
• Subgroup analyses will be performed for the proportion of patients with plasma HIV 1 RNA <50

copies c/mL, study outcomes and unadjusted difference in proportion of patients with plasma HIV 1 RNA <50 copies c/mL between treatment arms forest plot at Week 24,Week 48, Week 96 and Week 144 endpoints only.

Sensitivity and Supportive Analyses

1. A sensitivity analysis will be performed on the proportion of patients with plasma HIV-1 RNA <50 c/mL endpoint at Week 48, Week 96 and Week 144. For this analysis, patients who withdrew from the study due to the prolongation of the study as defined in the protocol amendment 6 (as captured on the study discontinuation CRF) will be removed from the denominator in both arms. The purpose of this analysis is to investigate the impact of snapshot categorisation bias that may be introduced in the event of a higher withdrawal rate in the TBR arm. The Cochran-Mantel-Haenzel approach will then be followed as described in the primary analysis section.
2. A sensitivity analysis based on the <50 HIV-1 RNA endpoint will be performed based on the same analysis for the following endpoints:

- Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL at Week X
- Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and Target Not Detected Status at Week X
- Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and Target Not Detected Status at Week X by Baseline Third Agent Class

3. 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 (i.e. drug-related AE, protocol defined safety stopping criteria, or lack of efficacy)/efficacy related discontinuation (i.e. lack of efficacy).
- The detailed algorithm for TRDF (and ERDF) is listed in Section 13.10. 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 X will be presented by treatment group, along with estimated difference in proportions between treatment groups and its associated two-sided 95% CI.
- A sensitivity analysis similar to that described in 1) above will be considered for the TRDF/ERDF analyses in the event that withdrawal rates are higher in the TBR arm than the DTG + 3TC arm at Weeks 96 and 144. Details will be included in an amendment to the RAP.

Kaplan-Meier Plot of Time to Failure – Treatment/Efficacy-related discontinuation = Failure

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoint / Variables

Randomised Early Switch Phase analyses:

- Subjects with plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm at Week 24, 48, 96 and 144 by subgroup, based on the ITT-E population.
- Change from baseline CD4+ and CD4+/CD8+ ratio cell counts at Week 24, 48, 96 and 144 by subgroup.

These analyses have been specified in previous sections.

Analyses pertaining to the Late Switch Phase will be included in a RAP addendum.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 14: List of Data Displays.

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.

For Week 24, 48 96 and 144 analyses, outputs will be presented for the Early Switch Phase unless otherwise specified. Safety data presented through weeks 24,48, 96 and 144, will comprise all available safety data collected at that time point. For example, if some earlier recruiting patients have reached Week 36 and have available safety data, this will be presented for the Week 24 analysis.

In the event withdrawal rate due to PAM6 study design change is higher in the TBR arm, similar sensitivity analyses to that stated for the HIV-1 RNA <50 c/mL endpoint as detailed in Section 7.2.5.1 will be considered for some AE analyses at Weeks 96 and 144. Further details of which will be included in an amendment to the RAP.

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Safety Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Exposure				
Extent of Exposure	Y[1]			Y[2]
Adverse Events[3]				
All AEs by SOC and PT	Y			Y
All AEs by Maximum Grade[3]	Y[1]			Y[4]
Common AEs by freq [5]	Y	Y[6]		
Common Grade 2-5 AEs [5] by freq	Y			
Drug-Related AEs by SOC and PT	Y			Y
All Drug-Related AEs by SOC and Maximum Grade[3,8]	Y[1]			
Common non-Serious AEs by SOC and PT (subjects and number of occurrences)	Y			
Common Drug-related Grade 2-5 AEs [5]	Y			
Common Non-Serious AEs (FDAAA)	Y			
Cumulative AEs by visit	Y[1]			
Drug-Related AE leading to withdrawal from study	Y			
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment[8,9]	Y			Y
Serious and Other Significant AEs				
All SAEs by SOC	Y[1]			
Fatal SAEs	Y			Y
Non-Fatal SAEs				Y
All Drug-Related SAEs by	Y[1]			

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
SOC				
Drug-Related Non Fatal Serious AEs				Y
Drug-Related Fatal Serious AEs	Y			Y
Serious AEs by SOC and PT	Y			
Reason for Considering as a Serious Adverse Event				Y
Possible Suicidality-Related Adverse Event (PSRAE)				Y[7]
Cardiovascular events				Y

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- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Repeat for the Early + Late Switch Phase for the DTG + 3TC arm and for the Late Phase for the TBR arm.
2. Includes reason for any dose change/interruption in both arms.
3. For AEs reported more than once by a subject, the most severe intensity will be included.
4. One listing of all AEs including verbatim text and preferred term, one showing the relationship between verbatim text, preferred term and SOC and another giving subject numbers for individual all treatment emergent AEs.
5. Common AEs are those with >=2% (or 0.5% for drug-related grade 2-5 AEs if there are no such AEs >=2%) incidence in either treatment group summarised by frequency.
6. Plots of incidence rates and relative risk with 95% CI for DTG+3TG vs. TBR.
7. Four PSRAE listings: Event and Description (Section 1-Section 2), Possible Cause (Section 3), Section 4 and Section 5-Section 8.
8. Repeated by subgroup as well.
9. Repeated by maximum grade as well.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. An overview of the planned adverse events of special interest analyses are presented in Table 5 and full details of the planned displays are provided in Appendix 14: List of Data Displays.

Table 5 Overview of Planned Adverse Events of Special Interest Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Adverse Events of Special Interest				
Characteristics of Post Baseline AESI	Y			
Onset and Duration of the First Occurrence of Post Baseline AESI	Y			
Total Duration of Post Baseline AESI	Y			
Post Baseline Depression, Suicidal and Self-Injury Adverse Events by AE of Special Interest, Maximum DAIDS Toxicity Grade, and Prior History of Depression and Anxiety	Y			

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and Liver Function tests will be based on GSK Core Data Standards. Table 6 provides an overview of the planned laboratory analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 6 Overview of Planned Laboratory Analyses

Endpoint	Absolute				Change from Baseline						Max Post BL			
	Summary		Individual		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	F	L	T	F	F	L	T	F	T	F	F	L
Laboratory Values Over Time														
Clinical Chemistry	Y			Y[1]	Y									

Endpoint	Absolute				Change from Baseline						Max Post BL			
	Summary		Individual		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	F	L	T	F	F	L	T	F	T	F	F	L
Lipids (%)					Y[4]									
Fasted Lipid (Triglycerides, LDL, HDL and TC and TC/HDL)	Y[4]				Y[4]									
Hematology	Y			Y[1]	Y									
Urine Dipstick				Y[1]										
Urine Concentration				Y[1]										
Liver Chemistries												Y[2]		
NCEP shifts in lipids					Y[4]	Y[3,4]					Y[4]	Y[3,4]		
Total Cholesterol/HDL ratio					Y[4]	Y[3,4]					Y[4]	Y[3,4]		
Biomarkers														
Bone biomarkers				Y	Y			Y	Y	Y				
Bone biomarkers (%)								Y						
Renal biomarkers				Y	Y			Y	Y	Y				
Renal biomarkers (%)								Y						
Inflammation Biomarkers				Y	Y			Y	Y	Y				
Telomere length				Y	Y			Y						
Change from baseline in HOMA-IR at Week 24, 48, 96 and 144				Y	Y			Y	Y[5]	Y				
HOMA-IR vs weight scatter plot							Y[6]							
HOMA-IR shift table[7]					Y						Y			
Emergent Laboratory Toxicities														
Clinical Chemistry											Y			
Hematology											Y			

Endpoint	Absolute				Change from Baseline						Max Post BL			
	Summary		Individual		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	F	L	T	F	F	L	T	F	T	F	F	L
Fasting LDL Cholesterol Abnormalities of Grade 2 or Greater											Y[4]			
AST, ALT and Total Bilirubin Maximum Post-Baseline Emergent Toxicity By Baseline Hepatitis C Status											Y			

NOTES :

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- 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. Listings for subjects with abnormalities for potential clinical concern/importance, defined as any Grade1-5 toxicity.
2. Scatter plot of baseline vs. maximum post-baseline for ALT. Scatter plot of maximum ALT vs. maximum Bilirubin.
3. Bar chart for LDL, HDL, TC, Trig and TC/HDL ratio.
4. Subjects on lipid-lowering agents at baseline are not included in summaries, see Lipids. Section 13.7.2 for more details.
5. Not performed at Week 24.
6. A scatter plot of change in HOMA-IR (y-axis) vs change in weight (x-axis) at Weeks 24, 48, 96 and 144.
7. See Section 13.6.4 for more details.

Statistical Analyses
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) at Weeks 24, 48, 96 and 144
Covariates & Factors
• Baseline 3rd Line Agent • CD4+ cell count (continuous) • Age (continuous) • Sex (Female vs. Male) • Race (White, Black or African American, Asian, Other) • BMI (continuous) • Smoking status (Never vs. Former vs. Current Smoker) • Vitamin D use (Yes vs. No)
Data Handling
• No multiple imputation techniques will be used to deal with the missing data.

Statistical Analyses
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 analysed for each bone biomarker for the comparison between DTG + 3TC and TBR. • 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 value (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 value for the endpoint can vary between visits (i.e. baseline value*visit interaction will be included in the model). • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Section 13.13: 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 – TBR) 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.
Sensitivity Analyses
• 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
• Not applicable

Statistical Analyses
Endpoints
• Change from baseline in renal biomarkers (serum Cystatin C, Urine Beta-2 Microglobulin /Urine Creatinine ratio (mg/mmol), urine albumin/creatinine ratio, urine protein/creatinine ratio, urine phosphate, eGFR (based on CKD-EPI-creatinine and CKD-EPI-cystatin C), serum creatinine and Urine Retinol Binding Protein 4/Urine Creatinine ratio (ug/mmol)) at Weeks 24, 48, 96 and 144
Covariates & Factors
• Baseline 3rd Line Agent

Statistical Analyses
• CD4+ cell count (continuous) • Age (continuous) • Sex (Female vs. Male) • Race (White, Black or African American, Asian, Other) • BMI (continuous) • Presence of diabetes mellitus (DM) (Yes vs no) • Presence of Hypertension (Yes v no)
Data Handling
• No multiple imputation techniques will be used to deal with the missing data.
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 analysed for each renal biomarker for the comparison between DTG + 3TC and TBR. • Using OC dataset, the Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline renal 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 value (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 value for the endpoint can vary between visits (ie. baseline value*visit interaction will be included in the model). • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Section 13.13: 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 – TBR) 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.
Sensitivity Analyses
• Line plots of LS means with 95% confidence intervals for Adjusted Mean Change from Baseline will be generated for each treatment group by visit

Statistical Analyses
Subgroup Analyses
• Not applicable

Statistical Analyses
Endpoints
• Change from baseline in inflammatory biomarkers (Interleukin-6 (IL-6), High-sensitivity C reactive protein (hs-CRP), D-dimer, Soluble CD14 (sCD14), Soluble CD163 (sCD163)) at Weeks 48, 96 and 144
Covariates & Factors
• Baseline 3rd Line Agent • CD4+ cell count (continuous) • Age (continuous) • Sex (Female vs. Male) • Race (White, Black or African American, Asian, Other) • BMI (continuous) • Smoking status (Never vs. Former vs. Current Smoker) • HCV-coinfection (Yes vs. No)
Data Handling
• No multiple imputation techniques will be used to deal with the missing data.
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 analysed for each inflammatory biomarker for the comparison between DTG + 3TC and TBR. • Using OC dataset, the Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline inflammatory biomarker value at as a covariate, with visit as the repeated factor. • The model will make no further assumptions about the correlations between a subject's value (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 value for the endpoint can vary between visits (i.e. baseline value*visit interaction will be included in the model). • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Section 13.13: 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

Statistical Analyses
difference (DTG + 3TC – TBR) 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.
Sensitivity Analyses
• Not applicable 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
• Not applicable

Statistical Analyses
Endpoints
• Change from baseline in HOMA-IR at Weeks 48, 96 and 144 (refer to Section 13.6.4 for details of derivation)
Covariates & Factors
..
• Baseline 3rd Line Agent • CD4+ cell count (continuous) • Age (continuous) • Sex (Female vs. Male) • Race (White, Black or African American, Asian, Other) • BMI (continuous) • Presence of diabetes mellitus (DM) (Yes vs no) • Hypertension (Yes vs no)
Data Handling
• No multiple imputation techniques will be used to deal with the missing data.
Model Specification
• If change in HOMA-IR is not normally distributed 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 analysed for HOMA-IR for the comparison between DTG + 3TC and TBR. • Using OC dataset, the Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline HOMA-IR value at as a covariate, with visit as the repeated factor. • The model will make no further assumptions about the correlations between a subject's value (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 value for the endpoint can vary between visits (i.e. baseline value*visit interaction will be included in the model). • Interactions between treatment and each of the covariates will not be assessed.

Statistical Analyses
Model Checking & Diagnostics
• Refer to Section 13.13: 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 – TBR) and corresponding 95% confidence interval and p-value. • Note: If change from baseline in HOMA-IR data 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.
Sensitivity Analyses
• 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
• Not applicable

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results will be based on GSK Core Data Standards, unless otherwise specified. An overview of other safety analyses is presented in Table 7 and full details of the planned displays are presented in Appendix 12 Section 13.14: List of Data Displays. Note that ECGs and vital signs are only collected at screening, so will only be listed.

Table 7 Overview of Other Safety Analyses

Endpoint	Absolute				Change from Baseline					
	Summary		Individual		Summary		Individual		Stats Analysis	
	T	F	F	L	T	F	F	L	T	F
Other										
ECG at screening				Y						
Vital Signs				Y						
Liver Assessment	Y			Y						
Hepatobiliary Abnormality criteria	Y			Y[3]						
eC-SSRS	Y			Y[1]						
Subjects who became Pregnant				Y						
Patient Profiles				Y[2]						
Weight, by visit	Y				Y				Y	Y

Endpoint	Absolute				Change from Baseline					
	Summary		Individual		Summary		Individual		Stats Analysis	
	T	F	F	L	T	F	F	L	T	F
BMI, by visit	Y				Y				Y	Y
BMI category shifts from baseline					Y					

1. Includes Baseline and lists all visits for a subject who reports any ideation or behaviour at any visit.
2. Patient profiles for subjects meeting protocol defined liver stopping criteria and for patients with virologic failure. Patient profiles can also be provided for any other subjects.
3. All post-baseline abnormalities meeting Hepatobiliary Abnormality Criteria.

Statistical Analyses

Endpoints

- Change from baseline in weight (kg) and BMI (kg/m2) at Weeks 24, 48, 96 and 144

Covariates & Factors

- Baseline 3rd Line Agent
- CD4+ cell count (continuous)
- Age (continuous)
- Sex (Female vs. Male)
- Race (White, Black or African American, Asian, Other)

Data Handling

- No multiple imputation techniques will be used to deal with the missing data.

Model Specification

- If the change from baseline in weight (BMI for BMI analysis) is not normally distributed, 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 analysed for the comparison between DTG + 3TC and TBR.
- Using OC dataset, the Mixed Model Repeated Measures (MMRM), using the observed margins (OM) option, will adjust for treatment, covariates (listed above) and baseline weight (BMI for BMI analysis) value as a covariate, with visit as the repeated factor.
- The model will make no further assumptions about the correlations between a subject's weight (BMI for BMI analysis) (the correlation matrix for within-subject errors will be unstructured).
- The repeated measures analysis will assume that the treatment difference can vary between visits (i.e. 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 weight (BMI for BMI analysis) can vary between visits (i.e. baseline value*visit interaction will be included in the model).
- Interactions between treatment and each of the covariates will not be assessed.

Statistical Analyses
Model Checking & Diagnostics
• Refer to Section 13.13: 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 – TBR) and corresponding 95% confidence interval. • Note: If change in weight is 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 p-values.
Sensitivity Analyses
• 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
• Not applicable

9. OTHER STATISTICAL ANALYSES

9.1. Health Outcomes

9.1.1. Overview of Planned Analyses

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

Full details of data displays being presented in Section 13.14: List of Data Displays.

9.1.2. Planned Health Outcomes Statistical Analysis

Statistical Analyses
Endpoint(s)
• Change from baseline in EQ-5D-5L Utility Score at Weeks 24, 48, 96 and 144 • Change from baseline in EQ Visual Analogue Scale (VAS) at Weeks 24, 48, 96 and 144
Covariates & Factors
• Baseline 3rd Line Agent
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.

Statistical Analyses
• 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). • 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 – TBR) 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. • Figures to show the differences for subjects treated with DTG + 3TC compared to TBR in adjusted mean change from baseline with 95% CIs in Utility Score and Visual Analog Scale at each visit.

9.2. Virology

9.2.1. Overview of Planned Analyses

9.2.2. Planned Virology Statistical Analysis

The virology analyses of genotype and phenotype data will be based on the CVW and pPVW resistance populations. Please see Section 13.6.3 for details of the derivation of CVW. Please see Section 4 for details of the derivation of pPVW.

The CVW population will be based on subjects who have experienced a CVW at any point. Summary tables will present CVWs up to and including the time point of interest. CVWs must be confirmed within the phase in which they are reported. Listings will present CVWs occurring at any point with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 8 provides an overview of the planned virology analyses, with full details of data displays being presented in 13.14: List of Data Displays.

Table 8 Overview of Planned Virology Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Genotypic resistance				
Incidence of genotype at time of CVW[1]	Y[2]			Y[4]

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Phenotypic resistance[5]				
Incidence of phenotype at time of CVW[1]	Y[3]			Y[4]
INI replication capacity at time of CVW[1]				Y[4]
Fold Change at CVW	Y			
Net Assessment for Overall Susceptibility Score				
Overall Susceptibility Score (OSS)				Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- 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 time suspected virologic withdrawal criteria are met, and only tested once a subject confirms virologic failure at a subsequent visit.
2. Separate outputs for INI and NRTI/NNRTI/PI mutations
3. Separate outputs by phenotypic cut-off and by number of drugs to which subjects are resistant.
4. Produce for CVW and pPVW resistance populations.
5. Phenotypic data are not available for Baseline

10. PHARMACOKINETIC ANALYSES

Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4 in a sub-set of subjects. PK concentrations summaries for intense and Sparse PK will be performed.

10.1. Pharmacokinetic Analyses

10.1.1. Endpoint / Variables

10.1.1.1. Drug Concentration Measures

All PK concentration listing displays will be based on the Intensive and Sparse Pharmacokinetic populations. Concentrations of DTG and 3TC in plasma will be listed and summarized according to GSK standards, where applicable (Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic)).

DTG and 3TC concentration listings for the intensive PK population will be sorted by subject and time relative to dose, noting the study visit; summaries will be presented by study visit and time relative to dose.

DTG and 3TC concentration listings for the sparse PK population will be sorted by subject, study visit and time (or sampling window) relative to dose; summaries will be presented by study visit and time (or sampling window) for weeks 4, 24, 36, and 48 and by sampling window for weeks 8 and 12. Patient profiles refer to a collection samples collected sequentially with regard to the dosing schedule for the intensive PK population. Please refer to Section 13.3.2 for definitions of assessment windows for inclusion of PK concentrations in summary statistics. Please refer to Section 13.6.10 for rules around data derivation and imputation. Please refer to Section 13.6.5 for rules regarding exclusions for the intensive and sparse PK populations. Please refer to the protocol for more information regarding the sparse and intensive populations and dosing schedules.

10.1.1.2. Derived Pharmacokinetic Parameters for subjects participating in the intense PK sub-study

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin 5.3 or higher. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
Cmax	3TC and DTG maximum observed plasma concentration, determined directly from the concentration-time data
tmax	3TC and DTG time to reach Cmax, determined directly from the concentration-time

Parameter	Parameter Description
	data
Cτ	3TC and DTG observed plasma concentration at the end of the dosing interval, determined directly from the concentration-time data
C0	3TC and DTG observed pre-dose plasma concentration, determined directly from the concentration-time data
AUC(0-τ)	3TC and DTG area under the concentration-time curve in one dosing interval

10.1.2. Summary Measure

Not applicable.

10.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the Sparse and Intensive Pharmacokinetic Populations population, unless otherwise specified.

10.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

10.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 14: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Table 9 provides an overview of the planned analyses, with full details being presented in Appendix 14: List of Data Displays.

Table 9 Overview of Planned Pharmacokinetic Analyses

End Point	Untransformed							Log-Transformed			
	Stats Analysis			Summary		Individual		Summary		Individual	
	T	F	L	T	F	F	L	T	F	F	L
Intensive PK Concentrations											
Plasma 3TC Concentrations				Y	Y	Y	Y	Y	Y		
Plasma DTG Concentrations				Y	Y	Y	Y	Y	Y		
Sparse PK Concentrations											
Plasma 3TC Concentrations by Visit and sampling				Y	Y		Y				

End Point	Untransformed							Log-Transformed			
	Stats Analysis			Summary		Individual		Summary		Individual	
	T	F	L	T	F	F	L	T	F	F	L
window											
Plasma DTG Concentrations by Visit and sampling window				Y	Y		Y				
Intensive PK Parameters											
Plasma 3TC Parameters				Y			Y	Y			
Plasma DTG Parameters				Y			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.

11. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

If data permits, the sparse concentrations of 3TC and DTG collected at weeks 4, 8, 12, 24, 36 and 48 will be pooled with the intensive PK concentrations and potentially data from other studies to perform integrated PK analyses for DTG and 3TC. The primary goal of this analysis is to characterize the population pharmacokinetics of 3TC and DTG administered as a dual regimen maintenance treatment for HIV in participants who are virologically suppressed. The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of 3TC and DTG in this population will be investigated. The individual subject PK parameters will be estimated and documented for the purposes of any subsequent exposure response (PK/PD) analyses. The PopPK analyses for DTG and 3TC will be performed under a separate RAP and will be reported separately.

Further details to be included in a separate RAP.

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13. APPENDICES

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RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
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Section 13.15	Appendix 15: Example Mock Shells for Data Displays

13.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

13.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria (Significant Protocol Deviations) will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Subject deviates from any inclusion or exclusion criteria, as recorded in the eCRF
02*	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
03*	Interruption of IP 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 forms or eCRF CONMEDS forms in case commercial supply is used before study completion.
04	HIV immunotherapeutic vaccines used
05	Concurrent use of drugs that may decrease DTG concentration for >7 days: (Carbamazepine, Oxycarbamazapine, Phenobarbital, Phenytoin, St. John's wort (Hypericum perforatum), rifampin
06	Concomitant use of rifapentin
07	Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy used
08	Systemically administered immunomodulators used through Week 96 visit
09	HCV therapy based on interferon or any other medications that have a potential for adverse drug-drug interactions with study treatment
10	Concomitant use of acetaminophen in subjects with acute viral hepatitis
11	Dofetilide or pilsicainide used concurrently

Number	Exclusion Description
	with DTG
12	Subject's change (i.e., substitution or dose modification) of DTG, 3TC or component of TBR (except protocol allowed switches, e.g. switch of booster) but was not withdrawn from the study
13	Subject became pregnant while on study
14	Permanent discontinuation of IP/withdrawal due to a reason of “Protocol Deviation” (as recorded in the eCRF)

*Programmatically derived protocol deviations, which are defined in a separate protocol deviations specification document.

Please refer to Section 13.6.9 regarding cut-off dates regarding protocol deviations leading to exclusion from the per protocol set.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

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

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

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

Procedures	Screening Visit[a]	Open-label Randomised Early Switch Phase														Switch Visit	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week															
			4	8	12	24	36	48	60	72	84	96	108 (optional)[b]	120	132 (optional)[b]	144	148[c]	
Dispense PK Diary Card to intensive PK sub-set		X																
Sparse PK sample collection[ee]			X[gg]	X	X	X	X	X										
Dispense PK Diary Card to Sparse PK subjects		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, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PBMC = peripheral blood mononuclear cell, RNA = ribonucleic acid, RPR = rapid plasma reagin

a. As soon as all Screening results are available, randomization may occur.
b. This optional study visit is ONLY to be conducted in countries that require visits every 3 months per standard of care.
c. Subjects with plasma HIV-1 RNA ≥50 c/mL at Week 144 must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment. Subjects randomized to DTG + 3TC do not attend a Week 148 switch visit.
d. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for subjects with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the subject. Only the laboratory tests necessary to evaluate the AE/SAE/laboratory abnormality should be collected.
e. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1. Genotypic resistance testing results MUST be provided to ViiV after screening and before randomization.
f. Full medical history will be conducted prior to randomization and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
g. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. BMI will be calculated within the eCRF.
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale eC-SSRS, patient completed questionnaire) is to be administered prior to randomization.
i. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.

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

13.3. Appendix 3: Assessment Windows

Laboratory data, health outcomes, vital signs and genotypic and phenotypic data will be assigned to assessment windows according to actual dates rather than the nominal visit labels as recorded on the eCRF or in the laboratory database.

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.

13.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
All	All	-35	≤-4	≤-4	Screening
		1	-3	1	Day 1
		29	2	42	Week 4
		57	43	70	Week 8
		85	71	126	Week 12
		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, ...
		Study Day of last dose + 28	>Study Day of last dose +1	>Study Day of last dose +1	Follow-up

NOTES :

- For parameters which are not scheduled to be assessed at particular visits, the all-inclusive windows defined will still be used.
- Assessments at unscheduled visits will be included for 'any time On-treatment' time points and in data listings, as well as algorithms that make use of additional data (e.g., Snapshot).
- In the event a baseline value is missing, the latest pre-dose value prior to baseline will be used, notwithstanding this date occurring more than 3 days prior to baseline.

13.3.2. Definitions of Assessment Windows for Inclusion in the PK Analysis

The windows for inclusion of PK samples in summary statistics will be as follows:

- For intensive PK population (Week 4 only):
    - Samples collected 1 hour prior to dose for pre-dose sample
    - Samples collected within ±15 min of the 0.5, 1, 1.5, 2 H time points
    - Samples collected within ± 30 min of the 3h, 4h, 6h time points

- Samples collected within ± 1h for the 10h time point
- Samples collected within ± 2h for the 24 h time point

- For sparse PK population (Weeks, 4, 8, 12, 24, 36 and 48):
  - Samples collected within 1 hour prior to dose for pre-dose sample, within ±15 min of the 1H time point, within ±30 min window for 1-4hr post dose sample (i.e. between 0.5-4.5hr) and within ±60 min window for 4-12hr post dose sample (i.e. between 3-13hr).

Outside these allowed windows, concentration results will be flagged and NOT included in the calculations for the summaries, but will be used in listings.

Given steady state will be reached by Day 5, sparse PK analyses will use nominal visit windows for all sparse PK analyses.

13.4. Appendix 4: Study Phases and Emergent Adverse Events

13.4.1. Study Phases

Data collected from both arms up to and including the date of the Week 148 visit will be considered to be during the Early Switch Phase of the study. For subjects randomised to TBR, this will be the date of their Week 148 switch visit. For subjects randomised to DTG + 3TC, this will be calculated as 1035 (=[148x7] - 1) days after exposure start date.

For subjects randomised to DTG + 3TC, data collected from 1036 days after IP start day to Week 200 will be considered to be during the Late Switch Phase. Data collected after Week 200 will be considered to be during the Continuation Phase of the study.

For subjects randomised to the TBR arm, data collected from the date of the Week 148 switch visit to Week 200 will be considered to be during the Late Switch Phase of the study. Data collected after Week 200 will be considered to be during the Continuation Phase of the study.

Phase	Randomised Arm	Start	End
Early Switch Phase	DTG + 3TC	IP start date	IP start date + 1035 (=[148x7 – 1) or Withdrawal date before study day 1035
	TBR	Day 1 DOV	IP start date for switch to DTG + 3TC -1 or Withdrawal date before Week 148
Late Switch Phase	DTG + 3TC	IP start date +1036	Week 200 DOV -1 or Withdrawal date before Week 200
	TBR	IP start date for DTG + 3TC	Week200 DOV -1 or Withdrawal date before week 200
Continuation Phase	DTG + 3TC	Week 200 DOV	IP end date or Withdrawal date
	TBR	Week 200 DOV	IP end date or Withdrawal date

13.4.1.1. Study Phases 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

13.4.1.2. Study Phases for Adverse Events

For adverse events, partial AE start date will use imputation as described in 13.7.2.1. In the case of a completely missing start date, the event will be considered to have started On-treatment unless an end date for the AE is provided which is before start of study treatment; in such a case the AE is assigned as Pre-treatment.

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. 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 13.7.2.1
- 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.

13.4.1.3. Study Phases for Concomitant Medication

- Prior medications: Those taken (i.e., started) before the start date of investigational product.

- Concomitant medications: Those taken (i.e., started or continued) at any time between the start date and stop date of study treatment, inclusive. Prior medications that were continued during this period are also considered as concomitant medications.

- Post treatment medications: Those started after the stop date of study treatment. 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. For any medication starting on the same date as study treatment, it will be assumed that the medication was taken after the subject started taking study treatment.

Duration of episodes of concomitant medication will be calculated as medication stop date – medication start date, so long as the medication is defined as concomitant according to the rules above (and presented below in the scenario matrix). Durations will be left blank if stop date is missing.

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

- ART starting on 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.

- ART stopping on study treatment start date will only be considered as prior and not concomitant.

- Any ART entered on the Prior ART eCRF with partial end date will be assumed to have finished before Screening.

- ART stopped prior to screening includes all ART that has stopped prior to screening. All ingredients from any regimen that is switched to another regimen prior to the screening visit e.g. from TDF-based to TAF-based ART will be presented as having stopped.

- ART Medications received at or after Screening includes all ART that is either being received at the screening visit or is introduced at a later date. Note, for TBR patients this could be pre- or post- randomisation and for DTG + 3TC patients this can be pre-randomisation only; at randomisation and beyond for DTF + 3TC patients, ART is recorded as ‘study treatment’ and not recorded via ART-specific concomitant medication pages.

- ART Medications Received at Screening includes all ART that is ongoing at the screening visit 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

13.4.2. Combining Treatment Phases and States

On-treatment and Post-treatment assessments and events will be classified as occurring during the Early Switch, Late Switch or Continuation Phase of the study as follow:

- If a subject did not enter the Late Switch Phase, then any Post-treatment data will be assigned to the Early Switch Phase.
- If a subject did not enter the Continuation Phase, then any Post-treatment data will be assigned to the Late Switch Phase.
- For subjects who did enter the Continuation Phase, any Post-treatment data will be assigned to the Continuation Phase.

For concomitant medication, if there is a duration overlapping any period then this should be reflected such that a concomitant medication (at time of the data cut):

- Starting and ending before treatment start then phase is set to missing
- Is taken at any point during the early switch phase only then phase is set to “Early Switch Phase”
- Is taken at any point during the late switch phase only then phase is set to “Late Switch Phase”
- Is taken at any point during the continuation phase only then phase is set to “Continuation Phase”

- Is taken at any point across the early and late switch phases only then phase is set to “Early and Late Switch Phase”
- Is taken at any point across the late and continuation phases only then phase is set to “Late Switch and Continuation Phase”
- Is taken at any point across all three phases then phase is set to “Early Switch and Late Switch and Continuation Phase”.

13.4.3. Emergent Flag for Adverse Events

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

For adverse events, partial AE start date will use imputation as described in Section 13.7.2. 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.

For laboratory data, there will be no imputation of dates, which are expected to be fully complete and available in SDTM transfers. Any laboratory dates that are partially missing will be queried.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software and any other statistical reporting software required for the analysis and reporting will be used.	
Reporting Area	
HARP Server	uk1salx00175
HARP Compound	:\ARPROD\GSK3515864\mid204862*reporting_effort_number*
Analysis Datasets	
• Analysis datasets will be created 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 all reporting efforts.	

13.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

- All data displays will use the term “subjects” rather than “participants”.

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, unless otherwise stated.
- 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.
  - For [Insert Endpoint / Parameter] the following DP’s places will be applied:
  - Summary Statistics:
  - Listings:

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.
  - The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  - 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 13.3.
- However, data summaries will only report visits that are planned assessment time points for each parameter (according to the Time and Events table).
- Assessments at unscheduled visits will be included for ‘any time On-treatment’ time points and in data listings, as well any algorithms that make use of additional data (e.g., Snapshot).

Descriptive Summary Statistics	
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.	

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to PK One document (Standards for the Transfer and Reporting of PK Data using HARP). Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in a separate RAP
NONMEM/PK/PD File	Pop-PKPD file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in a separate RAP.
Pharmacokinetic Parameter Derivation	
PK Parameter to be	The PK parameters will be calculated by standard non-compartmental

Derived by Programmer	analysis according to current working practices and using WinNonLin v 5.2 or above. All calculations of non-compartmental parameters will be based on actual sampling times.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	If any PK parameter is not calculable because of NQs, it will be noted as NC (non-calculable) for the PKPar file and excluded (set to missing) from the PK parameter summary statistics. Refer to PK One document (Standards for the Transfer and Reporting of PK Data using HARP) for handling of non-numeric values in the parameter data.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

13.6. Appendix 6: Derived and Transformed Data

13.6.1. 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 • With the exception of the Snapshot endpoints, if after window assignment (see Section 13.3), there are multiple valid assessments of a parameter within the same window, then the following hierarchy will be used to determine the value to be used for summary statistics of observed values: o the assessment closest to the window target Study Day; o 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 (i.e. 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 initial study treatment start date: • Ref Date = Missing → Study Day = Missing • Ref Date < Treatment Start Date → Study Day = Ref Date –Treatment Start Date • Ref Data ≥ 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: Randomised Early Switch, Late Switch and Continuation Phase.
Study Drug
• Study Drug refers to either Investigational Product DTG + 3TC or TBR.

13.6.2. 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.
- GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  - Any subject with a missing date and month will have this imputed as '30th June'.
  - For analysis purposes, if a subject did not fail to meet inclusion criteria #1 (aged 18 years or older), then set any age imputed as <18 by the standard IDSL algorithm to 18. If the subject failed to meet inclusion criteria #1 then the imputed age will not be reset.
- 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:

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

for males:

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

where

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

TC = total serum cholesterol (mg/dL),

HDL = serum HDL cholesterol (mg/dL),

$SBPu$ = systolic blood pressure (mmHg) if 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)

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

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

Extent of Exposure

- Exposure to DTG + 3TC will be calculated from the IP eCRF pages. Exposure to TBR will be calculated from the CONART eCRF pages.

Demographics
• Subjects who were randomised to DTG + 3TC but did not report a IP start date will be categorised as having zero days of exposure. • Subjects who were randomised to TBR but withdrew on Day1 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 the actual exposure 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%). • Further clarifications on extent of exposure during the early and late switch phases will be provided in an addendum to the main RAP.
Strata
• For analysis purposes, randomisation strata will be used from that derived using eCRF data, even if this differs from the strata captured in IVRS. • For patients randomised to DTG + 3TC, baseline third agent class is collected on the prior ART history form. For patients randomised to current TBR, baseline third agent class is collected on the concomitant ART form. • Third agent class is identified using terms from the GSK Drug Dictionary

13.6.3. Efficacy

HIV-1 RNA
Snapshot
• It is intended to be primarily a virologic assessment of the endpoint, and as such follows a "virology first" hierarchy. • Virologic Success (e.g., <50 c/mL) or Virologic Failure within an analysis window (see Section 13.3) 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: $$\text{SnapshotRate} = \frac{\text{Number of responders in that analysis window}}{\text{Number of subjects in the analysis population}}$$ • Full details of the algorithm, including the handling of special cases, are included in Section 13.11 of note, the date at which the subject 'discontinue/withdrawn from the study' in the

HIV-1 RNA
Snapshot algorithm is the date of treatment discontinuation, rather than the date of study withdrawal,
Plasma HIV-1 RNA
• For summaries and analyses which use HIV-1 RNA level as a continuous measure, the logarithm to base 10 of the value will be used. • HIV-1 RNA results may be provided as censored values, such as <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. • Qualitive measures (i.e. "target detected" and "target non-detected") may also be provided by the laboratory vendor for values <40 c/ml. 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.
Confirmed Virologic Withdrawal (CVW), Suspected Virologic Withdrawal (SVW) and Precautionary Virologic Withdrawal (PVW) and potential Precautionary Virologic Withdrawal (pPVW)
Please refer to the protocol, Section 5.4.1 for more details of the derivation of CVW, PVW, pPVW and SVWs. PVW (leading to discontinuation) • May be met after two consecutive assessments with HIV-1 RNA >=50 and <200 c/mL without an identifiable, non-virologic cause (immunization, illness, nonadherence) and after discussion with Medical Monitor, OR • Will be met with three consecutive assessments with HIV-1 RNA >=50 and <200 c/mL pPVW • Will be met after two consecutive assessments with HIV-1 RNA >=50 and <200 c/mL SVW

HIV-1 RNA

- One assessment with HIV-1 RNA >= 200 c/mL after Day 1 with an immediately prior HIV-1 RNA <50 c/mL.

CVW

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) 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 re-test value (at CVW value), where Treatment Start < HIV-1 RNA sample date <= Treatment Stop Date + 1 (if Treatment Stop date exists). Note: study drug interruptions will not be taken into account when programmatically identifying CVW.
- Similarly, viral loads above criteria cut-offs resulting in SVW, CVW, PVW and pPVW need to have occurred post-Day 1 in order for the criteria to be met. For example an SVW can occur at Week 4 if Week 4 HIV-1 RNA >=200 i.e. the viral load above SVW criterion occurred post-Day 1.
- Additional guidelines specified in the protocol related to patient management only and will not be taken into account when programmatically identifying CVW.
- Please refer to Section 5.4.1 of the protocol for details of the derivation.

CDC HIV-1 Classification and HIV-associated conditions

- HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see protocol Section 13.7).
- Any 'other' conditions reported in the CRFs will be identified programmatically before being sent for clinical review to determine whether they should be classed as stage 3 associated conditions. Review will be ongoing and as a minimum will take place prior to each reporting

HIV-1 RNA
effort.

13.6.4. Safety

Extent of Exposure

- Exposure to DTG + 3TC will be calculated from the IP eCRF pages. Exposure to TBR will be calculated from the CONART eCRF pages. Number of days of exposure to study drug will be calculated as:
  Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1

For subjects randomised to DTG + 3TC at Day 1:

- For Early Switch Phase:
  - For patients completing the early switch phase Exposure = IP Start Date + 1035 (=[7*148] -1)
  - If a subject discontinues prior to Week 144, the IP Stop Date recorded in the eCRF will be used. A partial or missing IP stop date is handled as described in 13.7.2.1.
  - A Day 1 Date of Visit will be used for partial or missing IP start date.
- The overall exposure is calculated as
  - Exposure = IP Stop Date – IP Start Date + 1

For subjects randomised to TBR at Day 1:

- For Early Switch Phase:
  - Exposure = (IP Start Date – 1) – Day 1 DOV + 1
  - If a subject discontinues prior to Week 148, the Withdrawal Date (earliest of date recorded in disposition, study visit page and TBR stop date) recorded in the eCRF will be used in the following way:
    Exposure = (earliest of date recorded in disposition, study visit page and TBR stop date) – Day 1 DOV + 1
- After the Week 148 switch visit, the exposure to DTG + TBR is calculated as
  - Exposure = IP Stop Date – IP Start Date + 1.

- Duration of dosing in subject years will be calculated as the sum of subject duration of dosing in days (across all subjects)/365.25

- Subjects who were randomised to DTG + 3TC but did not report a IP start date will be categorised as having zero days of exposure.
- Subjects who were randomised to TBR but withdrew on Day1 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.
- An alternative calculation of exposure will be performed where the duration of any dosing interruptions based on eCRF data will be subtracted from the result above.

Extent of Exposure

- The ratio (percentage) of the actual exposure 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%).

Adverse Events

AE Severity – DAIDS Grading

- The DAIDS grading (VERSION 2.1, March 2017) 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
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

Laboratory Parameters

protocol.

- Toxicity grades provided by the central laboratory do not distinguish between abnormally high or low criteria, when both are relevant for a particular parameter.
- When summarising toxicity grades for such parameters, they will be categorised as to whether they are above or below the midpoint of normal range.

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

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
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 for the CKD-EPI creatinine equation:

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

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

Laboratory Parameters

CRT/κ or 1, and CRTmg/dL is serum creatinine concentration in mg/dL. The serum creatinine concentration in mg/dL is obtained from GSK standard units of μmol/L as CRTmg/dL =0.0113x CRTμmol/L.

CKD-EPI Cystatin C Equation (2012)

The following will be used for the CKD-EPI Cystatin C Equation:

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

Abbreviations / Units

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2

Scys (standardized serum cystatin C) = mg/l

min = indicates the minimum of Scys/0.8 or 1

max = indicates the maximum of Scys/0.8 or 1

age = years

Assays

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.
- 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.

BMI

- BMI classification is based on standard categories adopted by the WHO and FDA:
  < Normal = BMI of < 18.5 kg/m2
  Normal = BMI of 18.5 – 24.99 kg/m2
  Overweight = BMI of 25 – 29.99 kg/m2
  Obese = BMI of > 30 kg/m2

Note: Any shift to a higher BMI category counts as a shift to a 'worse category'.

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.
  - For summary tables at baseline, unscheduled repeat visits will not be summarised.
  - Relevant CRF pages will be completed based on the latest entry (if it was a positive alert).
- Late Day 1 assessments
  - Late DAY 1 assessments will be summarised as representing baseline status (i.e., treated as true DAY 1 assessments). Where this leads to multiple DAY 1 assessments, 'complete' assessments will be used over 'incomplete' assessments to represent baseline status. Such assessments will be considered DAY 1 if they occur by Day 14.
- Day 1 assessments performed at later visits
  - DAY 1 assessments on (or close to) study day 1 will be accepted as DAY 1 assessments (as above). For DAY 1 assessments performed at later visits, the 'Lifetime' assessment observation will not be summarised but the 'Within the past 2 months' assessment will be used as a surrogate for the later post-baseline visit

assessment.

Homeostatic model assessment-Insulin Resistance (HOMA-IR)

- HOMA-IR = (fasting plasma insulin (mU/L) * fasting plasma glucose (mmol/L)) / 22.5.
- HOMA-IR categories will be categorised as follows for the HOMA-IR shift table analysis:
  - <2
  - 2 to <3
  - 3 to <4
  - >=4

  HOMA-IR shift tables will be presented for baseline vs maximum value post-baseline and Week X, for Weeks 24, 48, 96 and 144. HOMA-IR categories will be broken down into: <2, 2 to <3, 3 to <4 and >=4.

All HOMA-IR analyses will be based on fasting values and only patients with post-baseline values will be included in analyses (i.e. patients with missing post-baseline HOMA-IR will not be included in summary tables or figures). Additionally, patients who are diabetic as captured on the medical history form at screening will be excluded from all HOMA-IR analyses. Finally, any patient who has taken an anti-diabetic medication (ATC code “A10” (**DRUGS USED IN DIABETES)**) as captured on the medical history form up to screening will be removed from the analysis.

13.6.5. Pharmacokinetic

General

- Data at specific timepoints of subjects who had major PK protocol deviations that could impact DTG or 3TC exposure will be removed, as detailed below:

PK Protocol Deviation	Populations Affected	Analysis Consideration
Non-fasting 8 hours pre-dose	- Intensive Concentration and Parameter Populations	Pre-dose and subsequent samples that day (not including 24 hours) will be excluded from summaries and figures but will be included in listings and flagged
Use of prohibited medications* at time of sample	- Intensive Concentration and Parameter Populations - Sparse Population	Samples will be excluded from summaries and figures but will be included in listings and flagged

- The Intensive pharmacokinetic population will be used for listing PK concentrations, calculating PK parameters, summaries of concentration-time data and plotting of individual concentration-time files for the intensive PK population.
- The Intensive Pharmacokinetic Parameter Population will be used for intensive PK parameter analyses
- If during clinical phase, 3 consecutive samples in any phase i.e.(Absorption, Distribution and Metabolism / Excretion) are found to be missing then data for that subject will not be included in PK and only the concentration data of that subject(s) will be presented
- The sparse pharmacokinetic population will be used for summarising PK concentrations.
- Listings will be based on the safety population, and only patients with a sample from the relevant dosing schedule will be presented in these listings.
- * Prohibited medications that could decrease DTG or 3TC exposure will be identified as leading to exclusion from PK summaries and figures if they are ongoing at the visit at which the analysis is taking place. If a prohibited medication has a non-missing start and stop date before, say Week 24, then there will be no exclusion from PK analyses at the Week 24 analysis. Prohibited medications are defined as follows:
    - Carbamazepine
    - Oxcarbamazepine
    - Phenobarbital

General
○ Phenytoin ○ Rifampin ○ Rifapentine ○ St. John's wort

13.6.6. Population Pharmacokinetic (PopPK)

Details will be provided in a separate RAP

13.6.7. Viral Genotyping and Phenotyping

Genotype

Amino Acid Changes

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

Representation of Amino Acid Changes

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

Resistance Associated Mutations

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

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A/I/K**, L74M, **E92Q/V**/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, **Y143C/H/R/K/S/G/A, P145S**, **Q146P**, **S147G**, **Q148H/K/R**, **V151**I/**L**/A, S153F/Y, **N155H/**S/T, E157Q, G163R/K, S230R,

Genotype

Amino Acid Changes

	R263K, L68V/I*, L74I*, E138T*, V151I*, G193E*

NOTES:

- Draft listing; may be modified in case of additional substantive data availability.
- 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.
- Each INI mutation listed had a score of ≥15. INI substitutions listed above in bold had a score of =60.

* 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).

- Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) as defined by the International Antiviral Society-USA (IAS-USA). The most up to date IAS-USA guidelines available at the time of DBF will be used in the analysis.

Class	Mutations
NRTIs	M41L, A62V, K65R/E/N, D67N, 69 insert, K70E/R, L74V, V75I, F77L, Y115F, F116Y,Q151M, M184V/I, L210W, T215Y/F, K219Q/E
NNRTIs	L100I, K101E/P, K103N/S, V106A/M, V108I, 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

Note: List generated from IAS_USA Guideline, - 2017 Drug Resistance Mutations Update Volume 24, Issue 4, December 2016/January 2017

Susceptibility Scores

Stanford Genotypic Susceptibility Score (GSS)

- To establish genotypic susceptibility to ART treatment, a genotypic sensitivity score will be calculated.
- Genotypic sensitivity to each drug will be assessed using the HIVdb, the Integrated Genotypic Resistance Interpretation System [Liu, 2006].
- In the 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).

Genotype

Amino Acid Changes

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.

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.
- For the DTG + 3TC arm a subject might have a M-GSS score of 0, 1 or 2, and in the TBR arm a subject might have a M-GSS score of 0, 1, 2, or 3 (since TBR is a 3-drug regimen).

Score	Sensitivity
1	Sensitive
0	Resistant

Phenotype

Phenotypic Susceptibility

- Phenotypic susceptibility to all licensed antiretroviral drugs and DTG will be determined using PhenoSense HIV assays from Monogram Inc. and will be reported as fold change (FC) in IC50 relative to wild-type control virus NL4-3, i.e., FC of sample virus = IC50 of sample virus/IC50 of control virus.
- Since the maximum assay limit for FC for each ART varies from subject to subject, FC values that are greater than the maximum assay limit (e.g., '>100') will be interpreted as having a value equal to the smallest maximum assay limit for that ART in the study population for data analysis. Censored values will be presented 'as is' in the listings.

- Phenotypic susceptibilities will be categorised according to FC (based on Monogram PhenoSense assay). Clinical cut-offs (where available) or biological cut-offs by PhenoSense will be used to define the phenotypic susceptibility of background treatment.
- Replication capacity is generated as part of standard phenotypic assays.

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

PSS with Full Sensitivity Only (PSSf)

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

PSS with Partial Sensitivity Included (PSSp)

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

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

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

a. clinical cutoff (lower cutoff – higher cutoff)

Phenotypic Susceptibility Score (PSS)

Net Assessment and Overall susceptibility of ARTs

- Net assessment is an assessment of antiviral activity of ARTs using both genotypic and phenotypic test results interpreted through a proprietary algorithm (from Monogram Biosciences) and provides the overall susceptibility of the drug (Note: partially sensitive and resistant calls are considered resistant in this analysis).
- For determining overall susceptibility of ARTs (OSS), a binary scoring system (0= resistant, 1=sensitive) for each antiretroviral agent was used and will be provided in the Monogram dataset. OSS will be calculated as the sum of the net assessment scores of ARTs comprising the 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 approach for Monogram resistance data analyses
• We might have resistance data that come from mixed datasets: PSGT, PSIN, GSIN (primary assays) vs PSGT+IN (secondary assay) • If one of the primary assay does not work for a specific timepoint, we might report the secondary assay if data is available. If all primary assays for a specific timepoint work then we report primary. For example, for baseline if the same assay section (PSGT, PSIN, GSIN) worked then we report primary. If at least one of PSGT or PSIN or GSIN didn't work then we report secondary PSGT+IN. • Secondary assay testing results might not always be available. **Background :** • DNA GenoSure Archive – only provides geno data for PRO/RT and Integrase • 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

13.6.8. 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 et al. 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. • Any missing values should be imputed using LOCF.
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).

Willingness to switch survey
• Assess the reason(s) for their participation and facilitate an understanding of subject's willingness to switch • A single item question prior to randomisation. • 7 reasons for willingness to participate in a clinical study where the current HIV medication may be switched check all that apply • Any missing values will remain missing

13.6.9. Cut-off date for protocol deviations

Cut-off date
The following rules should be used to calculate cut-off date for protocol deviations up to and including Week 24: • For subjects who have Week 24 viral load date (cut-off 1): - cut-off = Week 24 viral load date (used for snapshot algorithm) from LB (laboratory) dataset, or date of re-test date if patient had a re-test • For subjects who do not have Week 24 viral load date (cut-off 2): - cut-off date = 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 randomised to DTG + 3TC) or CM (for patients randomised to TBR), study treatment start date + 210* -1). **upper bound of week 24 window* Additional Statistical Programming Checks to identify 'Subjects with study withdrawal due to a reason of "Protocol Deviation" (as recorded in the eCRF) at or prior Week 24' will be performed. • Consider subjects that have discontinued from the study prior or at Week 24 with 'Protocol

deviation' as a reason in DS (study discontinuation).

- Cut-off date (cut-off 3):

- For subjects who have Week 24 viral load date -> cut-off = Week 24 viral load date (used for snapshot algorithm) from LB (laboratory) dataset.
- For subjects who withdrawn before Week 24 Snapshot HIVRNA sample taken or if missing data during week 24 window but on study-> cut-off = IP start date + 210* - 1

- Compare the PD occurrence date (Day of Study Discontinuation from DS) to cut-off date (see paragraph above, please note: cut-off rules 1 and 2 defined above do not apply here)
- If cut-off date ≥ PD occurrence date, then deviations will result in exclusion from the per protocol set.

*upper bound of week 24 window

Similar rules will be followed for Week 48, 96 and 144 and subsequent time points and will be detailed in a separate Protocol Deviation specification document. Please refer to latest version of the Protocol Deviation specification document prior to the analysis for full details of protocol deviation identification,

13.6.10. PK Data

Below Limit of Quantification (BLQ) concentrations from any of the sparse PK samples will be set to missing, regardless of the week of collection.

13.6.11. eCRF Baseline Third Agent Class Determination

Baseline third agent will be determined as the third agent ingredient:

- still being taken at randomisation for TBR patients
- discontinued immediately prior to randomisation for DTG + 3TC patients.

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	Subject study completion (i.e. as specified in the protocol) was defined as: • Randomly assigned to either treatment group, completed the Late Switch Phase at the Week 200 visit, and did not enter the Continuation Phase; • Subjects randomised to either treatment group, completed the Randomised Late Switch Phase at the Week 200 visit, entered and completed the Continuation Phase, defined as remaining on study until: o DTG and 3TC FDC tablet is locally approved for use as a 2-drug regimen, and available through public health services or through the subject's usual health insurance payer, or o the subject no longer derives clinical benefit, or o the subject meets a protocol-defined reason for discontinuation, or o 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.

13.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data are 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 are excluded from the table. • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should not be displayed as such.

Element	Reporting Detail
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 (or <400 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 13.11for full details
LOCF	• In the LOCF dataset, missing values will be carried forward from the previous, non-missing available on-treatment assessment.
Lipid LOCF	• If subjects initiate serum 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. • Missing assessments will not 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.
Observed Case (OC)	• This dataset uses only the data that is available at a particular timepoint, with no imputation for missing values.

13.7.2.1. Handling of Missing and Partial 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. Note Study Treatment DTG + 3TC is recorded on the Study Treatment CRFs and TBR treatment is recorded on the CONART CRFs.
Adverse Events and Clinical Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE and Clinical Event 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 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

Element	Reporting Detail
	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.

13.8. 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.

13.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

Details will be provided in a separate RAP.

13.10. Appendix 10: Time to Event Details

13.10.1. TRDF Detailed Steps

TRDF Detailed steps		
For studies that have a Late Switch or Continuation Phase, ensure only data pertinent to the analysis is included, see study RAP for definition of Treatment Phase. **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.** Randomised Period denotes period where subjects are still on their randomised treatment, prior to late switch of study treatment. This is also irrespective of blinding. Hence, Randomised Period also refers to Early Switch Phase.		
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 confirmed prior to cut-off used for the analysis) Then set **tempAVAL**= Study Day of SVW immediately preceding CVW		
1.1 CVW event date is after the upper bound of the analysis visit window i.e tempAVAL > upper bound of the analysis visit window for Week X	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 i.e tempAVAL ≤ upper bound of the analysis visit window for Week X	CNSR=0	EVNTDESC=CVW. AVAL= tempAVAL.
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)) Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Exposure domain]). Assumption: Study day of permanent treatment discontinuation is included in the definition to account for cases where discontinuation information is recorded later. This is a conservative approach consistent with treatment discontinuation preceding withdrawal.		
2.1 Study withdrawal is after the upper bound of the analysis visit window i.e tempAVAL > 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

i.e tempAVAL ≤ upper bound of the analysis visit window		Related AE. AVAL= tempAVAL
3: Subjects met protocol defined stopping criteria during the randomized period., (Based on disposition page) Then set **tempAVAL**=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Exposure domain]).		
3.1 Protocol defined stopping criteria were met after the upper bound of the analysis visit window i.e tempAVAL > 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 i.e tempAVAL ≤ upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria. AVAL=tempAVAL
4: Subjects with study withdrawal due to lack of efficacy during the randomized period. (Based on disposition page) Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Exposure		

domain])		
4.1 Study withdrawal is after the upper bound of the analysis visit window i.e tempAVAL > 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 i.e tempAVAL ≤ upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Lack of Efficacy AVAL= tempAVAL
If none of the above conditions met		
5: Subjects with study withdrawal for other reasons during the randomized period. (Based on disposition page) Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Exposure domain])		
5.1 Study withdrawal is after the upper bound of the analysis visit window i.e tempAVAL > upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
5.2 Study withdrawal is on or before the upper bound of the analysis visit window i.e tempAVAL ≤ upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to Study Discontinuation for Other Reasons. AVAL=tempAVAL

6: Subject completed the randomized period of the study. (Based on disposition page)	CNSR=1	EVNTDESC= Censored as completed the Randomized Period. AVAL= Date of end of Treatment Phase
7: Subject is ongoing in the study during the randomized period and have not yet completed the randomized period Assumption: this will only be in cases where the reporting effort/analysis is performed midway through the randomized period	CNSR=1	EVNTDESC= Censored due to data cutoff. AVAL=Upper bound of analysis visit window.

13.10.2. TRDF Detailed Steps for the Kaplan-Meier plot

TRDF Detailed steps		
The steps below are for the derivation of TRDF overall i.e. for the Kaplan-Meier plot only.		
Final step of the derivation is made in following order: [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. 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 confirmed prior to cut-off used for the analysis)	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])
If none of the above conditions met		
5: Subjects with study withdrawal for other reasons on or before the end of 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])
6: Subject completed the randomized period of the study. (Based on disposition page)	CNSR=1	EVNTDESC= Censored as completed the Randomized Period. AVAL= Date of completion of randomized study period
7: 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:
Randomised Period = Randomised Early Switch Phase
Efficacy visit windows should be used throughout for the upper bound of the analysis visit window
Subjects are considered to have completed the randomised period if they completed the Early Switch Phase.
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

13.10.3. ERDF Detailed Steps

Similar algorithm will be applied for ERDF analyses and Kaplan-Meier figure, where condition 2 and 3 in Section 13.10.1 and Section 13.10.2 will not be considered.

13.11. Appendix 11: Snapshot

Detailed Algorithm Steps

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
- Note: The only protocol-permitted substitutions are as follows:

  - A switch from a PI boosted with RTV to the same PI boosted with cobicistat is allowed.

  - A switch from a PI boosted with cobicistat to the same PI boosted with RTV is allowed.

Note the same process will be mapped out for Week 24.

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 background therapy
2. If ***permitted*** change in background therapy ***prior to*** Week 48 AND the latest on-treatment VL prior to/on the date of change is ≥ 50 c/m [a]	HIV1-RNA ≥ 50	Change in background therapy
3: If ***non-permitted*** change in background therapy ***during*** Week 48		
• Last on-treatment VL during Week 48 prior to/on the date of change ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window not below 50
• 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 background

		therapy
4: If ***permitted*** change in background therapy ***during*** Week 48 AND the last on-treatment VL prior to/on the date of change is ≥ 50 c/mL [a]		
4.1 this last on-treatment VL occurs prior to Week 48	HIV1-RNA ≥ 50	Change in background therapy
4. 2 this last on-treatment VL occurs during Week 48 but prior to/on the date of change	HIV1-RNA ≥ 50	Data in window not below 50
5: If none of the above conditions met		
5.1 VL available during Week 48		
• Last on-treatment VL during Week 48 ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window not below 50
• Last on-treatment VL during Week 48 <50 c/mL	HIV1-RNA < 50	
b. No VL during Week 48		
i. 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
ii. If subjects withdraw before/during Week 48 due to		
1. Safety reasons (e.g. AE/death, liver chemistry stopping criteria, renal toxicity withdrawal criteria, QTc withdrawal criteria et al, as recorded in eCRF Study Conclusion form)	No virologic data at Week 48 Window	Disc due to AE/death
2. Non-safety related reasons (e.g. Lack of efficacy, protocol deviation, withdrew consent, loss to follow-up, study closed/terminated, investigator discretion et al, as recorded in eCRF Study Conclusion Form)		
• Last on-treatment VL <50 c/mL OR no on-treatment VL available during study	No virologic Data at Week 48	Disc for other reasons

	Window	
• 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 while not below 50

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

Examples from FDA guidance

Data in Window

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

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

No Data in Window

Discontinued study due to Adverse Event or Death:

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

Discontinued for Other Reasons:

- Only patients who have achieved virologic suppression can be counted as *Discontinued for Other Reasons.*
- If a patient discontinues the study before the window because of *lack of efficacy* then the patient should be included in the HIV-RNA greater than or equal to 50 row and not in the Discontinued for Other Reasons row.
- If a patient discontinues because of *subject withdrew consent* and his or her HIV-1 RNA result at the time of discontinuation was equal to or above 50 copies/mL, then he or she should be categorized as HIV-RNA greater than or equal to 50 and NOT as Discontinued for Other Reasons.
- If a patient discontinued because of *Lost to Follow-Up* and the last HIV-RNA result was 49 copies/mL, then the patient can be categorized as Discontinued for Other Reasons.

- If patients changed background treatment — *not permitted by protocol*— they should be considered an efficacy failure and captured in the HIV-RNA greater than or equal to 50 copies/mL row.

On study but missing data in window:

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

Optimized Background Therapy Substitutions After Randomisation

- OBT substitutions (in-class or cross-class) permitted per protocol for documented toxicity reasons can be permitted on or before the first trial visit without penalty.
- If OBT substitutions for toxicity reasons occur after the first trial visit, then patients should be categorized as having HIV-RNA greater than or equal to 50 copies/mL if they have HIV-RNA above 50 copies/mL at the time of switch.

13.12. Appendix 12: Abbreviations & Trade Marks

13.12.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
DOV	Date of Visit
eCRF	Electronic Case Record Form
ERDF	Efficacy Related Discontinuation Failure
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomisation & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TAF	Tenofovir alafenamide fumarate
TBR	TAF based regimen

Abbreviation	Description
TFL	Tables, Figures & Listings
TRDF	Treatment Related Discontinuation Failure
GSK	GlaxoSmithKline

13.12.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
Epivir
Tivicay

Trademarks not owned by the GlaxoSmithKline Group of Companies
Monogram Inc
NONMEM
SAS
WinNonlin

13.13. Appendix 13: Model Checking and Diagnostics for Statistical Analyses

13.13.1. Statistical Analysis Assumptions

Endpoint(s)	Change from Baseline in bone/renal/inflammatory biomarkers, EQ5D, weight, BMI and HOMA-IR
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.
    - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
    - 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.

13.14. Appendix 14: List of Data Displays

13.14.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.n	1.01 to 1.n
Efficacy	2.01 to 2.n	2.01 to 2.n
Safety	3.01 to 3.n	3.01 to 3.n
Virology	4.01 to 4.n	4.01 to 4.n
Pharmacokinetic	5.01 to 5.n	5.01 to 5.n
Health Outcomes	6.01 to 6.n	6.01 to 6.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

13.14.2. Mock Example Shell Referencing

Non-IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 15: 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
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

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

13.14.3. Deliverables

Delivery [Priority] [1]	Description
DS [X]	During Study
IA SAC [X]	Interim Analysis Statistical Analysis Complete
SAC [X]	Final Statistical Analysis Complete

NOTES:

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

13.14.4. Study Population Tables

Note that where the Deliverable column states 'All', this refers to all reporting efforts i.e. Weeks 24, 48, 96 and 144.

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT-E	ES1	Summary of Subject Disposition for the Subject Conclusion Record		All
1.2.				No longer required	
1.3.	ITT-E	ES4	Summary of Subject Disposition at Each Study Epoch	Only present data for phases reached at time of analysis	Post-switch time points
1.4.	All Subjects Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		All
1.5.	All Subjects Screened	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		All
1.6.	ITT-E	POP_T1	Summary of Reasons for Withdrawal by Visit		All
Protocol Deviation					
1.7.	ITT-E	DV1	Summary of Important Protocol Deviations		All
1.8.	ITT-E	DV1	Summary of Protocol Deviations Leading to Exclusion from the Per-Protocol Population		All

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.9.	All Subjects Screened	SP1	Summary of Study Populations		All
1.10.				No longer required	
Demographic and Baseline Characteristics					
1.11.	ITT-E	DM1	Summary of Demographic Characteristics		All
1.12.	All Subjects Screened	DM11	Summary of Age Ranges		All
1.13.	ITT-E	DM5	Summary of Race and Racial Combinations		All
1.14.	ITT-E	DM6	Summary of Race and Racial Combinations Details		All
1.15.	ITT-E	POP_T2	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	POP_T3	Summary of Screening and Baseline Cardiovascular Risk Assessments		All
1.19.	ITT-E	POP_T4	Summary of Distribution of CD4+ Cell Count (cells/mm^3) Results at Screening and Baseline		All

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications, Medical Conditions					
1.20.	ITT-E	MH1	Summary of Current Medical Conditions		All
1.21.	ITT-E	MH1	Summary of Past Medical Conditions		All
1.22.	ITT-E	CM1	Summary of Concomitant Medications by Ingredient ATC Level 1		All
1.23.	ITT-E	CM8	Summary of Concomitant Medication Ingredient Combinations		All
1.24.	ITT-E	CM1b	Summary of Concomitant Medication by Combination Term ATC Level 1		All
1.25.	ITT-E	POP_T5	Summary of Antiretroviral Therapy Stopped Prior to Screening		All
1.26.	ITT-E	POP_T5	Summary of Antiretroviral Therapy Received at or After Screening		All
1.27.	ITT-E	MH4	Summary of Current Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		All
1.28.	ITT-E	MH4	Summary of Past Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		All
1.29.	ITT-E	POP_T6	Summary of Lipid Modifying Agent Use at Baseline		All

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.30.	ITT-E	POP_T6	Summary of Lipid Modifying Agent Use Starting Post-Baseline		All
1.31.	ITT-E	POP_T7	Summary of History of Depression and Anxiety at Baseline		All
1.32.	ITT-E	POP_T8	Summary of Baseline Third Agent Class		All
1.33.	ITT-E	NS1	Summary of Number of Subjects by Country and Site ID		All
1.34.	ITT-E	POP_T9	Summary of Number of Subjects Attending Nominal and Actual Analysis Visits		All
1.35.	Intensive PK Parameter	DM1	Summary of Demographic Characteristics – Intensive PK Parameter Population		24
1.36.	ITT-E	POP_T10	Summary of Antiretroviral Therapy at Screening by Regimen		All

13.14.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Analysis					
2.1.	ITT-E	EFF_T1	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	EFF_T1	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥ 50 c/mL at Week X – Snapshot Analysis		All
2.3.	ITT	EFF_T1	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	EFF_T2	Summary of Study Outcomes (Plasma HIV-1 RNA ≥ / < 50 c/mL) at Week X – Snapshot Analysis		All
2.5.	Per-Protocol	EFF_T2	Summary of Study Outcomes (Plasma HIV-1 RNA ≥ / < 50 c/mL) at Week X – Snapshot Analysis		All
2.6.	ITT	EFF_T2	Summary of Study Outcomes (Plasma HIV-1 RNA ≥ / < 50 c/mL) at Week X – Snapshot Analysis		All
2.7.	ITT-E	EFF_T1	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥ 50 c/mL at Week X – Snapshot Analysis (Sparse Data Sensitivity Analysis)		All

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Efficacy Analyses					
2.8.	ITT-E	EFF_T2	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X – Snapshot Analysis		All
2.9.				No longer required	
2.10.				No longer required	
2.11.	ITT-E	EFF_T5	Summary of Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL by Visit – Snapshot Analysis		All
2.12.	ITT-E	EFF_T5	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit – Snapshot Analysis		All
2.13.	ITT-E	EFF_T6	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X by Subgroup – Snapshot Analysis		All
2.14.				No longer required	
2.15.	ITT-E	EFF_T3	Summary of Study Outcomes (Plasma HIV-1 RNA ≥ / < 50 c/mL) at Week X by Subgroup - Snapshot Analysis		All
2.16.	ITT-E	EFF_T8	Summary of Change from Baseline in Plasma HIV-1 RNA (log10 c/mL) by Visit		All
2.17.	ITT-E	EFF_T9	Summary of Change from Baseline in in CD4+ count (cells/mm3) by Visit		All

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	ITT-E	EFF_T9	Summary of Change from Baseline in in CD4+/CD8+ count ratio (cells/mm3) by Visit		All
2.19.	ITT-E	EFF_T10	Summary of Post-Baseline HIV-1 Associated Conditions Including Recurrences		All
2.20.	ITT-E	EFF_T10	Summary of Post-Baseline HIV-1 Associated Conditions Excluding Recurrences		All
2.21.	ITT-E	EFF_T11	Summary of Post-Baseline HIV-1 Disease Progressions		All
2.22.	ITT-E	EFF_T12	Cumulative Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit		All
2.23.	ITT-E	EFF_T13	Distribution of Quantitative Plasma HIV-1 RNA Results at Suspected and Confirmed Virologic Withdrawal		All
2.24.	ITT-E	EFF_T14	Summary of Change from Baseline in in CD4+ count (cells/mm3) at Week X by Subgroup		All
2.25.	ITT-E	EFF_T15	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal at Week X - Treatment Related Discontinuation = Failure		All
2.26.	ITT-E	EFF_T15	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal at Week X - Efficacy Related Discontinuation = Failure		All

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27.	ITT-E	EFF_T2	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL at Week X – Snapshot Analysis		All
2.28.	ITT-E	EFF_T2	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and Target Not Detected Status at Week X - Snapshot Analysis - ITT-E		All
2.29.	ITT-E	EFF_T5	Summary of Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL by Visit - Snapshot Analysis		All
2.30.	ITT-E	EFF_T5	Summary of Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and Target Not Detected Status by Visit - Snapshot Analysis		All
2.31.	ITT-E	EFF_T3	Summary of Study Outcomes (<40 c/mL) at Week X - Snapshot		All
2.32.	ITT-E	EFF_T3	Summary of Study Outcomes (<40 c/mL and Target Not Detected Status) at Week X - Snapshot		All
2.33.	ITT-E	EFF_T6	Summary of Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and Target Not Detected Status at Week X by Baseline Third Agent Class -Snapshot Analysis - ITT-E		All
2.34.	ITT-E	EFF_T14	Summary of Change from Baseline in CD4+/CD8+ Count Ratio (cells/mm3) at Week X by Subgroup		All

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.35.	ITT-E	EFF_T2	Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week X – Snapshot Analysis - Withdrawal Bias Sensitvity Analysis		48, 96 and 144

13.14.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Analyses					
2.1	ITT-E	EFF_F1	Proportion (95% CI) of Subjects with HIV-1 RNA >=50 c/mL by Visit – Snapshot Analysis		All
Secondary Efficacy Analyses					
2.2.	ITT-E	EFF_F1	Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL by Visit – Snapshot Analysis		All
2.3.	ITT-E	EFF_F2	Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week X by Subgroup – Snapshot Analysis		All
2.4.	ITT-E	EFF_F3	Individual Plasma HIV-1 RNA and CD4+ Profiles by Visit for subjects with at least one viral load ≥50 c/mL		All
2.5.	ITT-E	EFF_F3	Individual Plasma HIV-1 RNA and CD4+/CD8+ count ratio Profiles by Visit for subjects with at least one viral load ≥50 c/mL		All
2.6.	ITT-E	EFF_F4	Kaplan-Meier Plot of Time to Failure - Treatment Related Discontinuation = Failure (TRDF)		All
2.7.	ITT-E	EFF_F4	Kaplan-Meier Plot of Time to Failure - Efficacy Related Discontinuation = Failure (ERDF)		All

13.14.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	Safety	SAFE_T1	Summary of Extent of Exposure to Investigational Product / Study Treatment – Early Switch Phase		All
3.2.	Safety	SAFE_T1	Summary of Extent of Exposure to Investigational Product / Study Treatment – Early and Late Switch Phase		Post-switch only
3.3.	Safety	SAFE_T1	Summary of Extent of Exposure to Investigational Product / Study Treatment - Late Switch Phase		Post-switch only
Adverse Events (AEs)					
3.4.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		All
3.5.	Safety	AE5B	Summary of Adverse Events by System Organ Class, Maximum Toxicity and Subgroups	See Section 5.4.2 for information on which subgroups to present	All
3.6.	Safety	AE5A	Summary of All Adverse Events by Maximum Grade		All
3.7.	Safety	AE3	Summary of Common (>=2%) Adverse Events by Overall Frequency		All
3.8.	Safety	AE3	Summary of Common (>=2%) Grade 2-5 Adverse Events by Overall Frequency		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term		All
3.10.	Safety	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade		All
3.11.	Safety	AE15	Summary of Common (>=2%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subject and Occurrences)		All
3.12.	Safety	AE3	Summary of Common (>=1%) Drug-Related Grade 2-5 Adverse Events by Overall Frequency		All
3.13.	Safety	SAFE_T2	Summary of Cumulative Adverse Events by Visit		All
Serious and Other Significant Adverse Events					
3.14.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		All
3.15.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term /by Overall Frequency		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.16.	Safety	AE5A	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Maximum Grade		All
3.17.	Safety	SAFE_T3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Subgroup	See Section 5.4.2 for information on which subgroups to present	All
3.18.	Safety	AE3	Summary of Serious Adverse Events by System Organ Class		All
3.19.	Safety	AE1	Summary of Fatal Serious Adverse Events		All
3.20.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class		All
3.21.	Safety	AE3	Summary of Drug-Related Fatal Serious Adverse Events		All
Laboratory: Chemistry					
3.22.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit		All
3.23.	Safety	SAFE_T3	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities		All
3.24.	Safety	LB1	Summary of Fasting Lipids by Visit		All
3.25.	Safety	LB1	Summary of Change from Baseline in Fasting Lipids by Visit		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.26.	Safety	LB1	Summary of Lipids Percentage Changes from Baseline by Visit – Early Switch Phase		All
3.27.	Safety	LB1	Summary of Lipids Percentage Changes from Baseline by Visit – Early and Late Switch Phase	Late switch only	All Late switch
3.28.	Safety	SAFE_T4	Summary of Changes in NCEP Lipid Baseline Category to Maximum Post-Baseline Category	Triglycerides, LDL Cholesterol, Total Cholesterol (mmol/L) NCEP Categories	All
3.29.	Safety	SAFE_T4	Summary of Changes in HDL Cholesterol NCEP Baseline Category to Minimum Post-Baseline Category		All
3.30.	Safety	SAFE_T5	Summary of Changes in NCEP Lipid Baseline Category to Week X Category	Triglycerides, HDL, LDL Cholesterol, Total Cholesterol (mmol/L) NCEP Categories	All
3.31.	Safety	SAFE_T6	Summary of Changes in TC/HDL Ratio Category to Maximum Post-Baseline Category		All
3.32.	Safety	SAFE_T6	Summary of Changes in TC/HDL Ratio Baseline Category to Week X		All
3.33.				No longer required	
Laboratory: Hematology					
3.34.	Safety	LB1	Summary of Hematology Changes from Baseline		All
3.35.	Safety	SAFE_T3	Summary of Maximum Post-Baseline Emergent Hematology Toxicities		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Urinalysis					
3.36.				No longer required	
Biomarkers					
3.37.	Safety	LB1	Summary of Change from Baseline in Bone Biomarkers by Visit		All
3.38.	Safety	LB1	Summary of Change from Baseline in Renal Biomarkers by Visit		All
3.39.	Safety	LB1	Summary of Change from Baseline in Renal Biomarkers - Loge Transformed Data by Visit		All
3.40.	Safety	LB1	Summary of Change from Baseline in Inflammatory Biomarkers		48, 96, 144
3.41.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline Bone Biomarkers - MMRM		All
3.42.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline in Renal Biomarkers – MMRM		All
3.43.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline in Renal Biomarkers - Loge Transformed Data - MMRM		All
3.44.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline in Inflammatory Biomarkers at Week X – ANCOVA		48, 96, 144

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)					
3.45.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		All
3.46.	Safety	LIVER10	Summary of Subjects Meeting Hepatobiliary Abnormality Criteria – All Post-Baseline Abnormalities		All
Other					
3.47.	Safety	SAFE_T8	Summary of Positive Suicidal Indication Alerts Based on eCSSRS by Visit		All
3.48.	Safety	SAFE_T9	Summary of Subjects with C-SSRS Suicidal Ideation or Behaviour at Baseline		All
3.49.	Safety	SAFE_T9	Summary of Subjects with Post Baseline C-SSRS Suicidal Ideation or Behaviour		All
3.50.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Anxiety Adverse Events of Special Interest		All
3.51.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Depression Adverse Events of Special Interest		All
3.52.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Suicidality and Self Injury Adverse Events of Special Interest		All
3.53.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Insomnia Adverse Events of Special Interest		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.54.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Rash Adverse Events of Special Interest		All
3.55.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Nightmare/Abnormal Dreams Adverse Events of Special Interest		All
3.56.	Safety	SAFE_T10	Summary of Characteristics of Post Baseline Drug Hypersensitivity Adverse Events of Special Interest		All
3.57.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Anxiety Adverse Events of Special Interest		All
3.58.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Depression Adverse Events of Special Interest		All
3.59.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Suicidality and Self Injury Adverse Events of Special Interest		All
3.60.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Insomnia Adverse Events of Special Interest		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.61.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Rash Adverse Events of Special Interest		All
3.62.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Nightmare/Abnormal Dreams Adverse Events of Special Interest		All
3.63.	Safety	SAFE_T11	Summary of Onset and Duration of the First Occurrence of Post Baseline Drug Hypersensitivity Adverse Events of Special Interest		All
3.64.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Anxiety Adverse Events of Special Interest		All
3.65.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Depression Adverse Events of Special Interest		All
3.66.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Suicidality and Self Injury Adverse Events of Special Interest		All
3.67.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Insomnia Adverse Events of Special Interest		All
3.68.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Rash Adverse Events of Special Interest		All
3.69.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Nightmare/Abnormal Dreams Adverse Events of Special Interest		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.70.	Safety	SAFE_T12	Summary of Total Duration of Post Baseline Drug Hypersensitivity Adverse Events of Special Interest		All
3.71.	Safety	SAFE_T15	Summary of Post Baseline Depression and Suicidal and Self-Injury Adverse Events by AE of Special Interest, Maximum DAIDS Toxicity Grade, and Prior History of Depression and Anxiety		All
3.72.	Safety	SAFE_T13	Summary of AST, ALT and Total Bilirubin Maximum Post-Baseline Emergent Toxicity by Baseline Hepatitis C Status		All
3.73.	Safety	LB1	Summary of Change from Baseline in HOMA-Insulin Resistance at Week X		All
3.74.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline in HOMA-Insulin Resistance at Week X - ANCOVA		48, 96, 144
3.75.	Safety	LB1	Summary of Change from Baseline in Weight (kg) by Visit		All
3.76.	Safety	LB1	Summary of Change from Baseline in BMI (kg/m2) by Visit		All
3.77.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline in Weight (kg) - MMRM		All
3.78.	Safety	SAFE_T7	Statistical Analysis of Change from Baseline in BMI (kg/m2) - MMRM		All
3.79.	Safety	SAFE_T14	Summary of BMI Shifts from Baseline to Worst Post-Baseline Result		All

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.80.	Safety	LB1	Summary of Change from Baseline in Telomere Length at Week X		144
3.81.	Safety	SAFE_T16	Summary of HOMA-IR Shifts from Baseline to Week X		All
3.82.	Safety	SAFE_T16	Summary of HOMA-IR Shifts from Baseline to Worst Post-Baseline Result		All
3.83.	Safety	New shell	Sumamry of Chemistry by Visit		All
3.84.	Safety	New shell	Summary of Hematology by Visit		All
3.85.	Safety	New shell	Summary of Weight (kg) by Visit		All
3.86.	Safety	New shell	Summary of BMI (kg/m2) by Visit		All

13.14.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE10	Plot of Common (>=2%) Adverse Events and Relative Risk		All
Laboratory					
3.2.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT		All
3.3.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin		All
Other					
3.4.	Safety	SAFE_F1	Bar Chart of Triglycerides, LDL Cholesterol and Total Cholesterol (mmol/L) NCEP Categories at Week X vs. Baseline		All
3.5.	Safety	SAFE_F1	Bar Chart of Triglycerides, LDL Cholesterol and Total Cholesterol (mmol/L) NCEP Categories at Baseline vs. Maximum Post-Baseline		All
3.6.	Safety	SAFE_F4	Bar Chart of HDL Cholesterol NCEP Categories at Baseline vs. Minimum Post-Baseline		All
3.7.	Safety	SAFE_F2	Line Plot of Adjusted Mean (95% CI) Change from Baseline in Renal Biomarkers Over Time — MMRM		All
3.8.	Safety	SAFE_F3	Line Plot of Ratio of Geometric Means (95% CI) in Renal Biomarkers Over Time - Loge Transformed Data - MMRM		All

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	Safety	SAFE_F2	Line Plot of Adjusted Mean (95% CI) of Change from Baseline in Bone Biomarkers Over Time — MMRM		All
3.10.	Safety	SAFE_F5	Line Plot of Adjusted Mean (95% CI) of Change from Baseline in Weight (kg) Over Time — MMRM		All
3.11.	Safety	SAFE_F5	Line Plot of Adjusted Mean (95% CI) of Change from Baseline in BMI (kg/m2) Over Time — MMRM		All
3.12.	Safety	SAFE_F1	Bar Chart of Total Cholesterol/HDL Ratio Categories at Week X vs. Baseline		All
3.13.	Safety	SAFE_F1	Bar Chart of Total Cholesterol/HDL Ratio Categories at Baseline vs. Maximum Post-Baseline		All
3.14.	Safety	New shell	Scatter Plot of Change in HOMA-IR vs. Change in Weight at Week X		All
3.15.	Safety	SAFE_F2	Line Plot of Adjusted Mean (95% CI) Change from Baseline in Inflammatory Biomarkers Over Time — MMRM		48, 96, 144
3.16.	Safety	SAFE_F2	Line Plot of Adjusted Mean (95% CI) Change from Baseline in HOMA-IR — MMRM		48, 96, 144

13.14.9. Virology tables

Virology: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	CVW	VIR_T1	Summary of INI Mutations at Baseline and Time of CVW at or prior to Week X		All
4.2.	CVW	VIR_T2	Summary of Major Mutations of NRTI, NNRTI and PI Classes by region at Baseline and Time of CVW at or prior to Week X		All
4.3.	CVW	VIR_T3	Summary of Genotype at Baseline and Time of CVW by Genotypic Cut-Off at or prior Week X		All
4.4.	CVW	VIR_T4	Summary of Phenotype at Baseline and Time of CVW by Phenotypic Cut-off at or prior Week X		All
4.5.	CVW	VIR_T5	Summary of Phenotype at time of CVW by Number of Drugs to Which Subject are Resistant at or prior Week X		All
4.6.	CVW	VIR_T6	Summary of Fold Change to DTG, 3TC, TDF and FTC at - Time of CVW at or prior to Week X		All
4.7.	ITT-E	VIR_T7	Summary of Subject Accountability: Genotypes Available at or prior to Week X		All
4.8.	ITT-E	VIR_T8	Summary of Subject Accountability: Phenotypes Available at or prior to Week X		All

13.14.10. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Intensive PK - PK Concentration Data					
5.1	Intensive Pharmacokinetic Concentration Population	PK01	Summary of Plasma DTG PK Concentration-Time Data by Nominal Time Relative to Dose	Sorted by Study Visit and Time relative to Dose	24
5.2	Intensive Pharmacokinetic Concentration Population	PK01	Summary of Plasma 3TC PK Concentration-Time Data by Nominal Time Relative to Dose	Sorted by Study Visit and Time relative to Dose	24
Intensive PK Derived Parameters					
5.3.	Intensive PK Parameter Population	PK_T1	Summary of untransformed and $\log_e$-transformed Derived Plasma DTG PK Parameters		24
5.4.	Intensive PK Parameter Population	PK_T1	Summary of untransformed and $\log_e$-transformed Derived Plasma 3TC PK Parameters		24

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Sparse PK - PK Concentration Data					
5.5.	Sparse PK Population	PK01	Summary of Plasma DTG PK Concentration-Time Data by Visit and Nominal Time Relative to Dose	Sorted by Study Visit and/or Time (window) relative to Dose	24, 48
5.6.	Sparse PK Population	PK01	Summary of Plasma 3TC PK Concentration-Time Data by Visit and Nominal Time Relative to Dose	Sorted by Study Visit and/or Time (window) relative to Dose	24, 48
5.7.	Sparse PK Population	PK_T2	Summary of Pre-dose Fasted Status by Visit	Week 24 fasting status considers to whether a patient was fasted for at least 6 hours pre-dose, whereas Week 4 fasting status considers if the pre-dose sample from the PK diary is fasted.	24, 48
5.8.	Sparse PK Population	PK_T2	Summary of Pre-dose Fed Status by Visit	Week 24 fasting status considers to whether a patient was fasted for at least 6 hours pre-dose, whereas Week 4 fasting status considers if the pre-dose sample from the PK diary is fasted.	24, 48

13.14.11. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Intensive PK - PK Concentration Data					
5.1.	Intensive Pharmacokinetic Concentration Population	PK24	Individual Plasma DTG Concentration-Time Plots (linear and Semi-log)	Overlay all individual profiles	24
5.2.	Intensive Pharmacokinetic Concentration Population	PK24	Individual Plasma 3TC Concentration-Time Plots (linear and Semi-log)	Overlay all individual profiles	24
5.3.	Intensive Pharmacokinetic Concentration Population	PK17	Mean Plasma DTG Concentration-Time plots (linear and semi-log)		24

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.4.	Intensive Pharmacokinetic Concentration Population	PK17	Mean Plasma 3TC Concentration-Time plots (linear and semi-log)		24
5.5.	Intensive Pharmacokinetic Concentration Population	PK18	Median Plasma DTG Concentration-Time plots (linear and semi-log)		24
5.6.	Intensive Pharmacokinetic Concentration Population	PK18	Median Plasma 3TC Concentration-Time plots (linear and semi-log)		24

13.14.12. Health Outcomes Tables

Health Outcomes : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
EQ-5D-5L					
6.1.	ITT(E)	HO_T1	Summary of EQ-5D Category Scores by visit – LOCF		All
6.2.	ITT(E)	HO_T2	Summary of EQ-5D Utility and Thermometer Scores by visit - LOCF		All
6.3.	ITT(E)	HO_T2	Summary of Change from Baseline in EQ-5D Utility and Thermometer Scores - LOCF		All
6.4.	ITT(E)	HO_T3	Statistical Analysis of Change from Baseline in EQ-5D Utility Scores – MMRM - LOCF		All
6.5.	ITT(E)	HO_T3	Statistical analysis of Change from Baseline in EQ-5D Thermometer Scores – MMRM - LOCF		All
Willingness to switch					
6.6.	ITT(E)	HO_T4	Summary of Reasons for Willingness to Switch – Early Switch Phase		All

13.14.13. Health Outcomes Figures

Health Outcomes : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
EQ-5D-5L					
6.1.	ITT(E)	HO_F1	Line Plot of Adjusted Mean (95% CI) Change from Baseline in EQ-5D-5L Utility Score Over Time – MMRM - LOCF		All
6.2.	ITT(E)	HO_F1	Line Plot of Adjusted Mean (95% CI) Change from Baseline in EQ-5D Thermometer Score Over Time – MMRM - LOCF		All

13.14.14. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Subjects Screened	ES7	Listing of Reasons for Screen Failure		All
2.	ITT-E	ES2	Listing of Reasons for Study Withdrawal		All
3.	ITT-E	SD3	Listing of Reasons for Study Treatment Discontinuation		All
4.	ITT-E	TA1	Listing of Planned Randomised and Actual Strata and Treatment Assignments		All
5.	ITT-E	POP_L1	Listing of Subjects Randomised but not Treated		All
Protocol Deviations					
6.	ITT-E	DV2	Listing of Important Protocol Deviations		All
7.	ITT-E	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		All
Populations Analysed					
8.	ITT-E	SP3a	Listing of Deviations Leading to Exclusion from the Per Protocol Population		All
Demographic and Baseline Characteristics					
9.	ITT-E	DM4	Listing of Demographic Characteristics		All
10.	ITT-E	DM10	Listing of Race		All

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Efficacy					
11.	ITTE	EFF_L1	Listing of Study Outcome (≥ / < 50 c/mL) at Week 48 – Snapshot Analysis		All
12.	ITTE	EFF_L2	Listing of Quantitative and Qualitative Plasma HIV-1 RNA Data		All
Exposure and Treatment Compliance					
13.	Safety	EX3	Listing of Exposure Data		All
Adverse Events					
14.	Safety	AE8	Listing of All Adverse Events		All
15.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		All
16.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		All
17.	Safety	PSRAE1	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1-Section 2)		All
18.	Safety	PSRAE3	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)		All
19.	Safety	PSRAE4	Listing of Possible Suicidality-Related Adverse Event Data (Section 4)		All
20.	Safety	PSRAE5	Listing of Possible Suicidality-Related Adverse Event Data (Section 5-Section 8)		All

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
21.	Safety	AE8	Listing of Fatal Adverse Events		All
22.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events		All
23.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		All
24.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		All
25.				No longer required	All
Hepatobiliary (Liver)					
26.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		All
27.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		All
All Laboratory					
28.	Safety	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance		All
29.	Safety	LB14	Listing of Laboratory Data with Character Results		All
30.	Safety	LB5	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		All

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
31.	Safety	VS4	Listing of Vital Signs		All

13.14.15. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
32.	All Subjects Screened	POP_L2	Listing of Subject Recruitment by Country and Site Number		All
33.	All Subjects Screened	ES9	Listing of Subjects Who Were Rescreened		All
34.	ITT(E)	POP_L3	Listing of Visit Dates		All
35.	All Subjects Screened	POP_L4	Listing of Study Populations		All
36.	ITT(E)	POP_L5	Listing of Hepatitis Test Results at Entry		All
37.	ITT(E)	CDC3	Listing of CDC Classification of HIV Infection at Baseline		All
38.	ITT(E)	RF2	Listing of HIV Risk Factors		All
39.	ITT(E)	POP_L6	Listing of Screening Cardiovascular Risk Assessment Data		All
40.	ITT(E)	MH2	Listing of Current and Past Medical Conditions at Baseline		All
41.	ITT(E)	POP_L7	Listing of Relationship Between Concomitant ATC Level 1, Ingredient and Verbatim Text		All

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
42.	ITT(E)	CM2	Listing of Concomitant Medications		All
43.	ITT(E)	CM2	Listing of Antiretroval Therapy Stopped Prior to Screening		All
44.	ITT(E)	CM2	Listing of Antiretroval Therapy Received at or After Screening		All
45.	ITT(E)	POP_L8	Listing of Relationship Between Concomitant ATC Level 4, Ingredient and Verbatim Text		All
Efficacy					
46.	ITT(E)	EFF_L3	Listing of Plasma HIV-1 RNA data for subjects with Confirmed Virologic Withdrawal		All
47.	ITT(E)	EFF_L4	Listing of CD4+ Cell Count Data		All
48.	ITT(E)	EFF_L5	Listing of CD8+ and CD4+/CD8+ Cell Count Ratio Data		All
49.	ITT(E)	HIV4	Listing of Stage 3 HIV-1 Associated Conditions		All
50.	ITT(E)	EFF_L6	Listing of Subjects Treatment-related discontinuation = Failure (TRDF)		All
51.	ITT(E)	EFF_L6	Listing of Subjects Efficacy-related discontinuation = Failure (ERDF)		All
Safety					
52.	Safety	EG3	Listing of ECG Findings		All
53.	Safety	SAFE_L1	Listing of Post Baseline Maximum ALT and Maximum Bilirubin		All

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
54.	Safety	SAFE_L2	Listing of Subjects Meeting Hepatobiliary Abnormality Criteria – All Post-Baseline Abnormalities		All
55.	Safety	SAFE_L3	Listing of C-SSRS Suicidal Ideation and Behaviour Data Alerts (4-9)		All
56.	Safety	SAFE_L4	Listing of C-SSRS Suicidal Ideation and Behaviour Data		All
57.	Safety	SAFE_L5	Listing of C-SSRS False Positive Alerts with Corresponding Reasons		All
58.	Safety	SAFE_L5	Listing of all C-SSRS True Positives, with Corresponding Reasons and AE or SAE status		All
59.	Safety	SAFE_L6	Listing of Subjects Who Became Pregnant During the Study		All
60.	Safety	SAFE_L7	Patient Profiles for Subjects Meeting Protocol Defined Liver Stopping Criteria		All
61.	Safety	SAFE_L7	Patient Profiles for Subjects Meeting Confirmed Virologic Withdrawal Criteria		All
62.	Safety	SAFE_L8	Listing of Cardiovascular Events		All
Intensive PK - PK Concentration Data					
63.	Safety	PK07	Listing of Plasma DTG PK Concentration-Time Data		24
64.	Safety	PK07	Listing of Plasma 3TC PK Concentration-Time Data		24

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Intensive PK Derived Parameters					
65.	Safety	PK13	Listing of Plasma DTG PK Parameters		24
66.	Safety	PK13	Listing of Plasma 3TC PK Parameters		24
Sparse PK - PK Concentration Data					
67.	Safety	PK07	Listing of Plasma DTG PK Concentration-Time Data		24, 48
68.	Safety	PK07	Listing of Plasma 3TC PK Concentration-Time Data		24, 48
Virology					
69.	CVW	VIR_L1	Listing of All Genotypic Data – CVWs		All
70.	pPVW	VIR_L1	Listing of All Genotypic Data – pPVWs		All
71.	CVW	VIR_L2	Listing of Genotype by Genotypic Cut-Off – CVWs		All
72.	pPVW	VIR_L2	Listing of Genotype by Genotypic Cut-Off – pPVWs		All
73.	CVW	VIR_L3	Listing of All Phenotypic Data – CVWs		All
74.	pPVW	VIR_L3	Listing of All Phenotypic Data – pPVWs		All
75.	CVW	VIR_L4	Listing of Replication Capacity – CVWs		All
76.	pPVW	VIR_L4	Listing of Replication Capacity – pPVWs		All

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
77.	CVW	VIR_L5	Listing of Net Assessment Score – CVWs		All
78.	pPVW	VIR_L5	Listing of Net Assessment Score – pPVWs		All
79.	CVW	VIR_L6		No longer required	All
80.	pPVW	VIR_L6		No longer required	All
81.	CVW	VIR_L7	Listing of Genotypic and Phenotypic Data for Subjects with Confirmed Virologic Withdrawal Criteria		All
82.	pPVW	VIR_L7	Listing of Genotypic and Phenotypic Data for Subjects with Potential Precautionary Virologic Withdrawal Criteria		All
Health Outcomes					
83.	ITT(E)	HO_L1	Listing of EQ-5D Category, Utility and Thermometer Scores		All
Other					
84.	Safety	SAFE_L9	Listing of Renal Biomarker Data		All
85.	Safety	SAFE_L9	Listing of Bone Biomarker Data		All
86.	Safety	SAFE_L9	Listing of Telomere Length Data		144
87.	Safety	SAFE_L9	Listing of HOMA-Insulin Resistance Data		All

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
88.	ITT-E	VIR_L7	Listing of Genotypic and Phenotypic Data for subjects Last on study VL>400 c/ml with resistance testing	For non-CVW and on-treatment patients	All
89.	ITT(E)	EFF_L3	Listing of Plasma HIV-1 RNA data for subjects with Potential Precautionary Virologic Withdrawal		All
90.	Safety	LB5	Listing of Hematology Laboratory Data for Subjects with Any Value of Potential Clinical Importance		All

13.14.16. Non-ICH Listings

Additional Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
91.	ITT(E)	POP_L9	Listing of History of Cardiac Therapeutic Procedures		All
92.	ITT(E)	POP_L10	Listing of Investigational Product Accountability		All

13.15. Appendix 15: Example Mock Shells for Data Displays

Mock shells are included in a separate document.