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

Title	:	Reporting and Analysis Plan Amendment for 200304: A Phase 3b, randomised, open-label study of the antiviral activity and safety of dolutegravir compared to lopinavir/ritonavir both administered with dual nucleoside reverse transcriptase inhibitor therapy in HIV-1 infected adult subjects with treatment failure on first line therapy
Compound Number	:	GSK1349572
Effective Date	:	08-MAY-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200304.
- This RAP is intended to describe the planned efficacy, safety & tolerability, virology and health outcome analyses required for the study.
- This RAP will be provided to the study team members to convey the content of IDMC, the Week 24 (interim) and Week 48 (primary) Statistical Analysis Complete (SAC) deliverables.

Author's Name and Functional Area:

[redacted] Principal Statistician (Clinical Statistics)	08-MAY-2017

Approved Via E-mail by

[redacted] Director Statistics (Clinical Statistics)	08-MAY-2017

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This RAP details all planned analyses and outputs required for the Week 24 and Week 48 Clinical Study Reports (CSR) of study 200304.
Protocol	• This RAP is based on the protocol amendment No. 1 (Dated: 30-APR-2014) of study 200304 (GlaxoSmithKline Document Number. : 2013N172672_01) and eCRF Version (Insert Version).
Primary Objective	• To demonstrate non-inferior antiviral activity at 48 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a WHO-recommended standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy.
Primary Endpoint	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm (Missing, Switch or Discontinuation = Failure) for the intent-to-treat exposed (ITT-E) population
Study Design	• Phase IIIb, randomised, open-label, active-controlled, multicenter, parallel group, non-inferiority study • Approximately 612 adult patients with confirmed virologic failure (HIV-1 RNA ≥400 c/mL on two occasions) on their first antiretroviral regimen consisting of one NNRTI + two NRTIs will be recruited. • Assuming a true response rate of 70% for both DTG and LPV/r arms, the study requires 306 subjects per arm to have 90% power with a 12% non-inferiority margin and a one-sided 2.5% significance level (see Section 8.2.1). • Subjects will be randomised 1:1 to receive DTG 50 mg once daily or LPV/RTV (800/200 mg once daily or 400/100 mg twice daily, in accordance with investigator decision and local label), each added to an investigator selected background regimen consisting of two NRTIs with at least one fully active NRTI. In consultation with the medical monitor, 3TC may be added as a third NRTI to a dual-NRTI background regimen in subjects with chronic HBV infection and evidence of HIV resistance to 3TC (e.g. M184V)
Planned Analyses	• The primary analysis at Week 48 will take place after the last subject completes 52 weeks on therapy (Day 1 to Week 48 plus a 4-week treatment extension). • An interim analysis and data cut will be conducted after the last subject completes 24 weeks on therapy, with the intent to provide an earlier assessment of efficacy to inform the Sponsor and clinicians. • An IDMC will be instituted to perform periodic reviews of the accumulating data to ensure that subjects are not being sub-optimally treated.
Analysis Populations	• The 'Intent-to-Treat Exposed Population' (ITT-E) consisting of all randomised subjects who receive at least one dose of study medication, assessed according to their randomised treatment regardless of the treatment they receive, will be the primary analysis population for evaluating efficacy.

Overview	Key Elements of the RAP
	• The 'Per-Protocol Population' consisting of subjects in the ITT-E population with the exception of major protocol violators, e.g. violations that could affect the assessment of antiviral activity will be used for sensitivity analyses of the primary efficacy endpoint. • The 'Safety Population' consisting of all subjects who receive at least one dose of IP, assessed according to the actual treatment received, will be used for evaluating safety and tolerability. Subjects will be analyzed according to the actual treatments received. • The 'Intent-to-Treat Population' consisting of all randomised subjects, assessed according to their randomised treatment even if no study treatment was taken or the wrong treatment was received, will be used for sensitivity analyses of the primary efficacy endpoint.
Hypothesis	• This study is designed to show that the antiviral effect of a regimen of DTG (administered once daily) + two NRTIs is non-inferior to LPV/RTV + two NRTIs; non-inferiority will be declared if the lower bound of the two-sided 95% CI for the difference in snapshot response rates (DTG – LPV/RTV) is greater than -12%. The primary analysis will be based on the ITT-E population using the Snapshot dataset at Week 48. The primary comparison will be made at a one-sided 2.5% level of significance.
Primary Analyses	• The primary endpoint will be analysed using a Cochran-Mantel-Haenszel stratified analysis, adjusting for baseline stratification factors. A point estimate and corresponding 95% confidence interval will be constructed for the adjusted difference in response rates between DTG and LPV/RTV treatment groups.
Secondary Analyses	• Secondary analyses will be conducted for additional efficacy, safety, health outcomes, and virologic endpoints.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 30/APR/2014).

The main changes included in RAP Amendment 1 are:

- HIV TSQ

The original RAP described analyses for the 10-item HIV TSQ, however the 14 -item HIV TSQ is being used in this study.

- Suspect Creatinine Samples

An issue was identified with the creatinine testing at the central laboratory. Sensitivity analyses will be conducted excluding any suspect creatinine samples from laboratory summaries including creatinine.

- Week 48 snapshot

Including a summary of week 48 snapshot outcomes in the Week 24 interim.

- Phenotype & genotype data for China subjects

Phenotype data may not be available for all subjects in China at the time of the Week 24 analyses. The China subjects may also have genotype data from Q2 and/or Monogram. In the event that subjects have both Q2 and Monogram data at a timepoint, the Monogram data will be used.

The main changes in RAP Amendment 2 are:

Following Protocol Amendment 2 (Dated: 19/Apr/2017) additional analyses have been included to account for subjects that switch from LPV/RTV to DTG or withdraw from the study due to the IDMC recommendation.

The planned summary by-visit CSSR has been replaced with the IDSL recommended summary.

Other minor changes have been included.

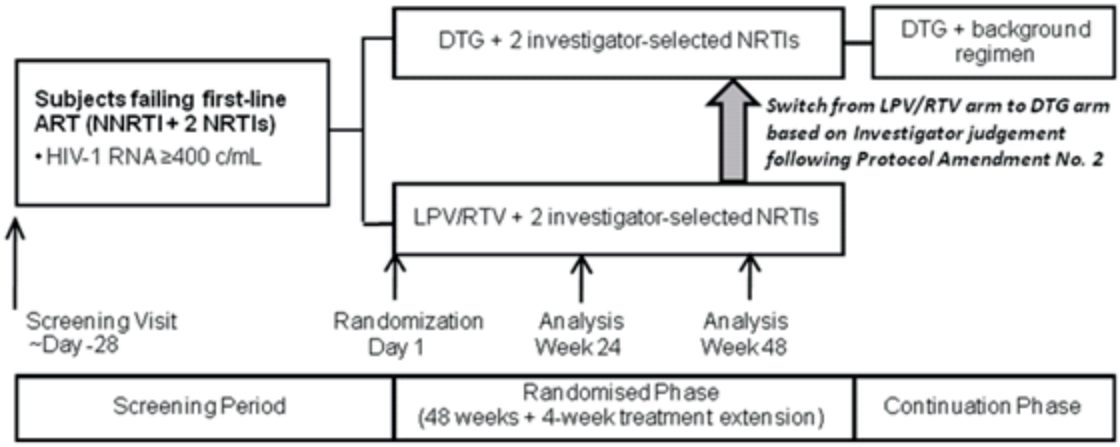
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To demonstrate non-inferior antiviral activity at 48 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a WHO-recommended standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy.	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm (Missing, Switch or Discontinuation = Failure) for the ITT-E population
Secondary Objectives	**Secondary Endpoints**
• To demonstrate non-inferior antiviral activity at 24 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a recommended WHO standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm
• To evaluate the antiviral and immunological activity and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG compared to LPV/RTV over time	• Proportion of subjects with plasma HIV-1 RNA <400 c/mL at Weeks 24 and 48 using the Snapshot algorithm; • Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related adverse

Objectives	Endpoints
	event, safety stopping criteria, and lack of efficacy); • Time to viral suppression (HIV-1 RNA <50 c/mL); • Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24 and 48; • Incidence of disease progression (HIV-associated conditions, AIDS and death).
• To assess the development of viral resistance in subjects meeting confirmed virologic withdrawal criteria;	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG, LPV/RTV and other on-study ART in subjects meeting confirmed virologic withdrawal criteria.
• To evaluate the safety, tolerability, and laboratory parameters of DTG compared to LPV/RTV over time	• Incidence and severity of AEs and laboratory abnormalities; • Absolute values and changes over time in laboratory parameters; • The proportion of subjects who discontinue treatment due to AEs.
• To compare the effects of DTG and LPV/RTV on fasting lipids over time	• Change from Baseline in fasting LDL cholesterol at Weeks 24 and 48; • Change from Baseline in fasting TC/HDL ratio at Weeks 24 and 48; • The incidence of maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24 and 48;
• To compare the effects of DTG and LPV/RTV on the occurrence of gastrointestinal adverse events over time	• The incidence of maximum post-Baseline emergent Grade 2 or greater drug-related diarrhoea by Weeks 24 and 48
• To compare the change in gastrointestinal symptom rating score for subjects treated with DTG and LPV/RTV over time	• Change from Baseline, using the Gastrointestinal Symptom Rating Scale (GSRS), at Week 4, Week 24, and Week 48
• To compare the satisfaction with treatment of patients with DTG compared to the LPV/RTV over time	• Change from Baseline in treatment satisfaction, using the HIV-Treatment Satisfaction Questionnaire (HIVTSQ), at Week 4, Week 24, and Week 48
• To compare patients' adherence with DTG compared to LPV/RTV over time	• Change from Baseline in adherence with treatment, using the Morisky 8-Item Medication Adherence Scale (MMAS-8), at Week 4, Week 24, and Week 48.
• To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG compared to LPV/RTV over time	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24 and 48 using the Snapshot algorithm

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• Phase IIIb, randomised, open-label, active-controlled, multicentre, parallel group, non-inferiority study in HIV-1 infected adult subjects with treatment failure on first line therapy • The 4-week treatment extension up to Week 52 is designed to collect a confirmatory viral load measurement at Week 52 in subjects presenting with HIV-1 RNA >50 c/mL at the Week 48 visit. According to the FDA's snapshot algorithm, which considers viral load measurements collected within a ± 6 week window around the Week 48 visit (including data from the Week 52 visit), if the retest viral load is < 50 c/mL then the subject will be classified as a virologic success in the primary analysis.
Dosing	• DTG 50 mg once daily or LPV/RTV (800/200 mg once daily or 400/100 mg twice daily, in accordance with investigator decision and local label)
Treatment Assignment	• Approximately N=612 Subjects will be randomised 1:1 to receive DTG 50 mg once daily or LPV/RTV (800/200 mg once daily or 400/100 mg twice daily, in accordance with investigator decision and local label), each added to an investigator selected background regimen consisting of two NRTIs with at least one fully active NRTI. In consultation with the medical monitor, 3TC may be added as a third NRTI to a dual-NRTI background regimen in subjects with chronic HBV infection and evidence of HIV resistance to 3TC (e.g. M184V). • GSK RandAll NG used to generate randomisation schedules, stratified by baseline HIV-1 RNA (Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and Baseline Number of fully active background NRTIs (<2 vs. 2)). • Centralised randomisation using GSK RAMOS for treatment allocation • Following the IDMC recommendation to switch LPV/RTV subjects to DTG, some subjects randomised to LPV/RTV may receive DTG post switch.
Interim Analysis	• An interim analysis will be conducted when all subjects have completed their Week 24 visit in order to provide an earlier assessment of efficacy to inform the Sponsor and clinicians.

Overview of Study Design and Key Features	
	• An IDMC will be utilised in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. Planned stopping guidelines and schedule for interim analyses are provided in Section 8.3.4.2 of the Protocol.

2.4. Statistical Hypotheses

This study is designed to show that the antiviral effect of a regimen of DTG (administered once daily) + two NRTIs is non-inferior to LPV/RTV + two NRTIs.

If r_d is the response rate on DTG + two NRTIs and r_a is the response rate on LPV/RTV + two NRTIs then the hypotheses can be written as follows:

$$H0: r_d - r_a \leq -12\% \qquad H1: r_d - r_a > -12\%.$$

3. PLANNED ANALYSES

3.1. Interim Analyses

The main analysis will be conducted to evaluate the primary objective of the protocol when all subjects have completed their Week 52 visit.

3.1.1. Week 24 data cut

An interim analysis will be conducted in order to provide an earlier assessment of efficacy to inform the Sponsor and clinicians after the following activities have been carried out:

1. All subjects have completed their Week 24 visit.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. Randomisation codes have been distributed according to RandAll NG procedures
4. All criteria for unblinding the randomisation codes have been met.

The analyses described in Section 7.1 and Section 8.1 will be performed with the sole difference being that the timepoint for these analyses will be Week 24 instead of Week 48.

No adjustment for multiplicity will be made for this analysis because the Week 24 endpoints represent secondary objectives for the study which are subordinate to the primary analysis at Week 48.

3.1.2. IDMC interim analyses

An IDMC has been instituted to provide independent review of the accumulating data, primarily to ensure subjects are not being sub-optimally treated in either arm.

Three formal interim analyses are planned for review by the IDMC (Table 1). Additional details are provided in the protocol and IDMC charter.

Table 1 Timing of Planned IDMC Interim Analyses and Stopping Guidelines

Interim Analysis	Timing	Endpoint	Evaluation (guideline)
#1	Once 100 subjects (total) have completed their Week 16 visit	Proportion of subjects with HIV-1 RNA <50 c/mL at Week 16 (Snapshot algorithm)	• Inferiority[a] (one-sided p<0.01)
#2	Once 300 subjects (total) have completed their Week 24 visit	Proportion of subjects with HIV-1 RNA <50 c/mL at Week 24 (Snapshot algorithm)	• Inferiority[a] (one-sided p<0.01)
#3	Once all subjects have completed their Week 24 visit	Proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm)	• Inferiority[a] (one-sided p<0.01) • Superiority[b] (one-sided p<0.0001)

a. Inferiority: significantly lower response rate with DTG than LPV/r.
b. Superiority: significantly higher response rate with DTG than LPV/r.

At time of finalisation of Protocol Amendment 2, the IDMC had completed interim analyses #1 and #2. Prior to interim analysis #3, the IDMC conducted an ad hoc review of trial data and observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. Interim analysis #3 will no longer take place.

3.2. Primary Analyses

The planned primary analyses will be performed after:

1. All subjects have completed their Week 52 visit as defined in the protocol.
2. All required database cleaning activities have been completed and database release and database freeze has been declared by Data Management.

3.3. Final Analyses

A final End-of-Study analysis will be conducted when all subjects have completed the study as defined in Section 3.1 of the Protocol.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Screened	• Comprised of all subjects screened for inclusion in the study. • Subjects may be re-screened once, for which they will receive a new subject number. • Only the latest re-screening data will be included in the screening population summaries/analyses but all screening data will be listed.	• Study Population
Intent-to-Treat Exposed (ITT-E)	• Comprise of all randomised subjects who receive at least one dose of study medication. • Subjects will be assessed according to their randomised treatment, regardless of the treatment they receive	• Efficacy • Health Outcome • Study population
Safety	• Comprise of all subjects who receive at least one dose of investigational product • Subjects will be analyzed according to the actual treatments received.	• Safety
Intent-To-Treat (ITT)	• Comprise of all randomised subjects. • Subjects will be assessed according to their randomised treatment even if no study treatment was taken or the wrong treatment was received.	• Sensitivity analyses of the primary efficacy endpoint
Week 36 Intent-to-Treat Exposed (MITT-E-36)	• Comprise all subjects in the ITT-E population randomised at least 36 weeks prior to 18 Jan 2017 (the last subject visit date for the Week 24 study report), excluding subjects still on-study in the randomised phase that had yet to provide a Week 36 HIV-1 RNA result by the Week 24 study report cutoff date.	• Week 36 snapshot outcomes for Week 24 study report.
Week 48 Intent-to-Treat Exposed (MITT-E-48)	• Comprise all subjects in the ITT-E population randomised at least 48 weeks prior to 18 Jan 2017 (the last subject visit date for the Week 24 study report), excluding subjects still on-study in the randomised phase that had yet to provide a Week 48 HIV-1 RNA result by the Week 24 study report cutoff date.	• Week 48 snapshot outcomes for Week 24 study report.
Per-Protocol	• Comprise of all subjects in the ITT-E population with the exception of major protocol violators, e.g. violations which could affect the	• Sensitivity analyses of the primary efficacy endpoint

Population	Definition / Criteria	Analyses Evaluated
	assessment of antiviral activity. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population). • Only protocol deviations that occur duing the randomised phase and before the outcome of interest may lead to exclusion from the PP population. For example, a subject with a protocol deviation between Week 24 and Week 48 would not be excluded from the Week 24 PP Population, due to this deviation, but would be excluded from the Week 48 PP Population	
Viral Genotypic	• Comprise of all subjects in the ITT-E population with available On-treatment genotypic resistance data at the time confirmed virologic withdrawal criterion is met	• Genotypic
Viral Phenotypic	• Comprise of all subjects in the ITT-E population with available On-treatment phenotypic resistance data at the time confirmed virologic withdrawal criterion is met	• Phenotypic

NOTES :

- Please refer to Appendix 17 List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population)].
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the per-protocol analysis are captured and categorised on the protocol deviations dataset. This dataset will be the basis for the summaries and listings of protocol deviations.

- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

- There are planned examination of covariates and subgroups.
- There are no planned adjustments made for multiple centres in this study.
- There are no planned adjustments for multiple comparisons or multiplicity.
- There are no PK analyses planned in this study.

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 11.2	Appendix 2: Time & Events
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Treatment States and Phases
Section 11.5	Appendix 5: Data Display Standards & Handling Conventions
Section 11.6	Appendix 6: Derived and Transformed Data
Section 11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
Section 11.8	Appendix 8: Values of Potential Clinical Importance
Section 11.9	Appendix 9: Multicenter Studies
Section 11.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata
Section 11.11	Appendix 11: Handling of Multiple Comparisons & Multiplicity
Section 11.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Section 11.13	Appendix 13: Snapshot
Section 11.14	Appendix 14: Q2 Creatinine Assay Accuracy Issue
Section 11.15	Appendix 15 Abbreviations & Trade Marks
Section 11.16	Appendix 16: Example SAS code for Additional Estimand 2
Section 11.17	Appendix 17: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

All displays are for the randomised phase only, unless specified otherwise. This means that the analysis will not be "windowed" at Week 24 ie all data collected up to the point of Database Freeze for Week 24will be included in summary statistics, which could be past week 24 for subjects enrolled early in the study. However, in the Week 48 report, the analysis will be "windowed", ie summary statistics will include data up to Week 52 only for both arms.

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

Table 3 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Randomisation			
Randomisation			Y[1]
Subject Disposition			
Study population[2]		Y	Y [3]
Summary of Subjects Enrolled by Country and Investigator [2]		Y	Y
Study recruitment by age (EMA)		Y	
Reasons for Screening Failures [2]		Y	Y
Subject Accountability by Phase (Overall, Randomised Phase, Continuation Phase)[4]		Y	
Reasons for Withdrawals by visit		Y	Y
Study visit dates			Y
Important Protocol Deviations		Y	Y
Deviations Leading to Exclusions from PP Population		Y	Y
Inclusion and Exclusion Criteria Deviations		Y	Y
Drug Accountability			
Investigational Product Accountability[5]			Y
Demography			
Demographics Characteristics[6]		Y	Y
Race & Racial Combinations[7]		Y x2	Y
CDC Classification of HIV Infection at Baseline		Y	Y
Baseline Cardiovascular Risk Assessments		Y	Y

Display Type	Data Display's Generated		
	Figure	Table	Listing
Plasma HIV-1 RNA Results at Screening and Baseline		Y	
CD4+ Cell Count Results at Screening and Baseline		Y	
Hepatitis Status at Entry		Y	Y
History of Cardiac Therapeutic Procedures			Y
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)		Y	Y[9]
Medical Conditions: sub-conditions (Current/Past)		Y	Y
Concomitant Medication (non ART)		Yx3[10]	Y[11,9]
Prior Antiretroviral Therapy (including Duration)		Yx4	Y[11]
Baseline Background Antiretroviral Therapy (including conART)		Y	Y[11]
Lipid Modifying Agent Use (Starting Baseline/Post-Baseline)		Y	Y
Virology			
Summary of the Number of Baseline Major Mutations Associated with the Resistance to NRTI, NNRTI, and PI drug classes		Yx2[8]	
Proportion of subjects without at least 1 fully active NRTI		Y	
Summary of Baseline Major NNRTI and NRTI Mutations		Y	
Summary of Stanford Baseline GSS to Background ART Regimen		Y	
Summary of Monogram Baseline GSS to Background ART Regimen		Y	
Summary of Baseline PSS to Background ART Regimen		Y	
Summary of Baseline OSS (Net Assessment) to Background Therapy		Y	
Summary of the Prevalence of HIV-1 Clades at Baseline by Frequency		Y	
Summary of First Line Regimen and Expected Second Line Regimen Using the WHO Algorithm[12]		Y	
Summary of Expected WHO Second Line vs. Background Regimen actually Taken[12]		Y	

NOTES:
Y = Yes display generated, T = Tables, L = Listings, IP = Investigational Product.

1. One listing of subjects randomised but not treated, and one listing of planned and actual treatment strata
2. All subject screened population
3. Listing of subjects excluded from any population will be generated only.
4. Subjects who have not been recorded as either completing or withdrawing from the study will be categorised as "Ongoing at time of the analysis" for summary purposes.
5. Dispensation information (dates and number of tablets dispensed and returned)
6. Gender, age, ethnicity, weight and height collected at screening (Day 1 for height)
7. 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.
8. Repeated for screening mutation for the Screen Failure population.
9. Repeated for Mexican subjects who experienced an adverse event at the End of Study SAC.
10. Three separate tables, summarised by Ingredient ATC Level 1, Ingredient combinations and Combination term ATC Level 1 (EG Includes single-ingredient medications with multi-ingredient medications labelled according to the sum of their ingredients, e.g., "TYLENOL Cold and Flu" would appear as "CHLORPHENAMINE MALEATE + DEXTROMETHORPHAN HYDROBROMIDE + PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE" under the ATC headings for "Nervous System" and "Respiratory System" (the combination's ATC classifications).)
11. One listing for concomitant non-ART medications, prior ART, background ART and one listing showing the relationship between verbatim text, ingredient and ATC Level 1.
12. WHO First and Second Line Regimens are defined in Appendix 6.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the Intent-to-Treat Exposed population, unless otherwise specified.

Summaries will be presented by treatment group with no total column.

The primary estimand and additional estimands for the Week 48 deliverables is presented in Table 4 below. For all estimands, the population of interest (ITT-E population), variable (plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm), and summary measure (proportion of subjects with response) will be the same. All estimands will account for discontinuation (other than due to IDMC recommendation) and non-permitted changes in background ART, as per the snapshot algorithm.

Table 4 Primary and Additional Estimands for the Week 48 Deliverable

Type of Estimand	Post-baseline Intervention of interest
Primary	No additional post baseline interventions considered. Subjects will be analysed according to their original treatment assignment regardless of treatment switch.

Type of Estimand	Post-baseline Intervention of interest
Additional	Additional Estimand 1 In addition, accounting for subjects that switch from LPV/RTV to DTG or withdraw from the study due to the IDMC recommendation (and subsequent Protocol Amendment 2). HIV-1 RNA values collected after treatment switching or discontinuation will be excluded from the analyses.
Additional	Additional Estimand 2 In addition, for subjects that switch from LPV/RTV to DTG or withdraw from the study due to the IDMC recommendation (and subsequent Protocol Amendment 2), their subsequent HIV-1 RNA values will be replaced with imputed values.

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

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm	Y[1]			Y[2]	Y[]		Y[2]
Treatment Heterogeneity across randomisation strata	Y						
Study Outcome based on the Snapshot				Y[4]			Y
Study Outcome based on the Snapshot by number of fully active background NRTIs				Y			
Proportion <50 c/mL at Week 48 by subgroup[5]				Y	Y[6]		
Summary of Study Outcomes based on the Snapshot at Week 48 by				Y			

Endpoint	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Subgroup							
Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm – Additional Estimand 1 [7]	Y[1]			Y[2]			
Study Outcome based on the Snapshot – Additional Estimand 1 [7]				Y[4]			
Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm – Additional Estimand 2 [7]	Y[1]			Y[2]			
Study Outcome based on the Snapshot – Additional Estimand 2 [7]				Y[4]			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. Statistical analysis displays will be generated using the 'Intent-to-Treat Exposed' (primary), 'Per-Protocol' and 'Intent-to-Treat' (sensitivity) populations.
2. Study outcomes (i.e., response below 50 c/mL, virologic failure or reason for no data in the window) based on the snapshot algorithm will be summarised and listed.
3. Line plots, with 95% confidence intervals, for the proportion of subjects below 50 c/mL by treatment group at each visit will be produced.
4. This summary will be produced for the week 24 study report.
5. Baseline demography (age, gender, race, country, CDC), HIV-1 subtype, Baseline CD4 and Baseline viral load, background ART (ABC+3TC vs not ABC+3TC).
6. Plot of 95% confidence intervals for the proportion of subjects below 50 c/mL by subgroup.
7. This summary will be produced for the week 48 study report.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm (Missing, Switch or Discontinuation = Failure) for the ITT-E population

Snapshot Dataset

- The Snapshot algorithm treats all subjects without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to the visit window) as non-responders, as well as subjects who switch their concomitant ART prior to the visit of interest in certain scenarios(Section 11.13).
- Switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and will not incur a penalty as per the FDA's Snapshot algorithm.
- Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is On-treatment within the visit of interest analysis window (see Section 11.4.2) Full details of the Snapshot algorithm are in Section 11.13.
- For subjects that switch from LPV/RTV to DTG, any subsequent HIV-1 RNA values will be left as is then virologic response or failure will be determined at Week 48 using snapshot algorithm, with subjects presented by their original randomised treatment..
-

Model Specification

- The primary endpoint will be analysed using a stratified analysis with Cochran-Mantel-Haenszel (CMH) weights, adjusting for Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and number of fully active background NRTIs in the background regimen (<2 vs. 2) at Baseline.
- The CMH estimate of the adjusted treatment difference will be calculated as a weighted average of strata-specific estimates of the treatment difference calculated within each of the following four Baseline analysis strata:
  - Plasma HIV-1 RNA ≤ 100,000 c/mL AND <2 fully active background NRTIs
  - Plasma HIV-1 RNA ≤ 100,000 c/mL AND 2 fully active background NRTIs
  - Plasma HIV-1 RNA > 100,000 c/mL AND <2 fully active background NRTIs
  - Plasma HIV-1 RNA > 100,000 c/mL AND 2 fully active background NRTIs
- If n_k is the number of DTG treated subjects, m_k is the number of LPV/RTV 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,

Primary Statistical Analyses

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

are CMH weights and d_k are estimates of the differences in response proportions between the two treatment arms, r_d-r_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. The full equation for this variance estimate is provided in the Appendix 6 (Section 11.6.5).

- For analysis purposes, fully active NRTI is defined at Baseline by the genotypic resistance reports of the central laboratory (or a laboratory contracted by the central laboratory) showing no evidence of full or of partial genotypic resistance for a given NRTI. If Baseline genotypic results are not available, then activity of the background regimen will be based on genotypic results at Screening.

Model Results Presentation

- Adjusted CMH estimate of the difference in the proportion of responders between each treatment group (DTG – LPV/RTV) and corresponding 95% confidence interval
- Non-inferiority will be concluded if the lower bound of the two-sided 95% confidence interval (CI) for the CMH adjusted difference in the proportion of patients who respond in the DTG group minus the proportion of patients who respond in the LPV/RTV group is greater than -12%.

Sensitivity and Supportive Statistical Analyses

- Treatment Heterogeneity across randomisation strata:
  - Randomization strata will be re-derived using Baseline values (Section 11.10.1).
  - The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable of the randomisation strata, with each categorical variable considered separately.
  - Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either rd or ra are zero or one, and tests will be one-sided.
  - Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported for each level of the categorical variable. Investigation of heterogeneity will be confined to the primary endpoint at week 24/48. Tests of homogeneity will be assessed at the one-sided 10% level of significance.
- Per-protocol population analysis:
  - To assess the impact of major 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 + two NRTIs is superior to

Sensitivity and Supportive Statistical Analyses

treatment with LPV/RTV + two NRTIs will be tested at the two-sided 5% level of significance. Superiority will be declared if the lower end of the confidence internal is above 0% for the ITT-E population analysis.

- 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, which therefore conservatively addresses any selection bias that may occur given the open-label study design.
- Exploration of Subgroups:
  - A simple analysis for all the subgroups listed in Section 11.10.1 will be performed. This will show the proportion of subjects with plasma HIV-1 RNA <50 c/mL at the time of analysis (Week 24/48) based on the Snapshot algorithm will be presented by treatment group.
  - Unadjusted difference in proportions between treatment groups and corresponding two-sided 95% CI will also be presented.by subgroup, and a 95% CI for the (unadjusted) treatment difference in each subgroup. These results will also be presented graphically.
  - If the basic summary suggests an interaction, then a corresponding summary of study outcomes (i.e., response below 50 c/mL, virologic failure or reason for no data in the window) by subgroup will be produced.

  Note: These subgroup analyses will be exploratory and likely underpowered so that interpretation may therefore focus on point estimates as well as the lower bounds of 95% CIs for the treatment differences and response rates. Additionally, multiple comparisons are being made which inflates the risk of false positive findings. Therefore, if consistent findings across the multiple comparisons were observed then these analyses would still be suggestive of a generalizable finding of non-inferiority.
- Supportive analysis for the Week 48 deliverable:
  - Additional Estimand 1: Following the IDMC recommendation (and subsequent Protocol Amendment 2), subjects may switch from LPV/RTV to DTG or withdraw from the study. Therefore, prior to the application of the Snapshot algorithm for the Week 48 deliverable, the following step will be undertaken:
    - For subjects that switch from LPV/RTV to DTG, any subsequent HIV-1 RNA values will be set to missing before the Snapshot algorithm is applied.
    - Note: for subjects that withdraw, the Snapshot algorithm will be applied as usual.
  - The population of interest (ITT-E population), variable (plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm), and summary measure (proportion of subjects with response) will be the same as that used for the primary endpoint.
  - Additional Estimand 2: For subjects that switch from LPV/RTV to DTG or withdraw from the study due to the IDMC recommendation (and subsequent Protocol Amendment 2), their subsequent HIV-1 RNA values will be imputed prior to determination of virologic response or failure at Week 48 using snapshot algorithm. See below for more details.

Additional Estimand 2 – Statistical Analyses

Endpoint

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

Covariates

- Baseline Plasma HIV-1 RNA (≤ vs. >100,000 c/mL)
- Baseline Number of Fully Active NRTIs in the Background Regimen (2 vs.<2)

Input Dataset, Imputation, and Statistical Analysis

- Select Log(HIV-1 RNA) samples and subset by treatment
- For the LPV/RTV arm:
    - For subjects that switch from LPV/RTV to DTG or withdraw from the study due to the IDMC recommendation, set any subsequent HIV-1 RNA values to missing
    - Using Markov Chain Monte Carlo methods, simulate 100 datasets replacing Below Limit of Quantification (BLQ) values with those from a Log(Uniform(0, BLQ) distribution. The BLQ value used for this step should be slightly below the actual BLQ cut-off so that response is correctly attributed when applying the snapshot algorithm later.
    - The statistical model used for the MI data generation will be the Markov Chain Monte Carlo (MCMC) method with for the data (covariates and Log HIV-1 RNA at Baseline, Week 4, Week 8, Week 16, Week 24, Week 36, Week 48, and Week 52) to produce a monotone pattern first, and then the imputation will continue using the Regression (REG) method for the monotone pattern with the same set of covariates.
        - A seed of 200304 will be used in the SAS program.
        - One imputation is required for each of the monotone and mean matching steps
        - Since it is likely that subject discontinuation or switches treatment due to IDMC recommendation will be based on observed viral load counts, the missing at random (MAR) assumption is appropriate
    - For subjects that originally had missing HIV-1 RNA data within the Week 48 window but did not discontinue or switch from LPV/RTV to DTG arms due to the IDMC recommendation, replace the imputed data with their original data. Data related to these subjects will be used only for the imputation of data for those that switch from LPV/RTV to DTG or withdraw from the study due to the IDMC recommendation
- Log(HIV-1 RNA) data for subjects randomised to the DTG arm is merged back onto each imputed dataset.
- Using Snapshot Algorithm, derive virologic response or failure at Week 48 using snapshot algorithm, as per Section 11.13, for each imputed dataset.
- For each imputed dataset, the endpoint will be analysed using a stratified analysis with Cochran-Mantel-Haenszel (CMH) weights, adjusting for Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and number of fully active background NRTIs in the background regimen (<2 vs. 2) at Baseline. This will be the same model as used for the primary endpoint.
- Wilson-Hilferty transformation will be applied to normalise the CMH statistic
- PROC MIANALYZE in SAS will be used to combine the 1,000 estimated proportion of subjects

Additional Estimand 2 – Statistical Analyses
with plasma HIV-1 RNA <50 c/mL and difference in proportions to produce one estimate with 95% CI and associated p-value for the adjusted difference between each treatment group at Week 48 See Appendix 16 for example SAS code.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the Intent-to-Treat Exposed population, unless otherwise specified.

All displays are for the randomised phase only, unless specified otherwise. This means that the analysis other than "by-visit" summaries will not be windowed at Week 24 (CVW, time to suppression). In other words, all data collected up to the point of DBF will be included in summary statistics, which could be past week 24 for subjects enrolled early in the study. However, at the Week 48 analysis, summary statistics will include data up to Week 52 for both arms.

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

Table 6 Overview of Planned Efficacy Analyses

Endpoints	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 24- Snapshot							
Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm[1]	Y			Y	Y		Y[2]
Treatment Heterogeneity across randomization strata	Y						
Study Outcome based on the Snapshot by number of fully active background NRTIs				Y			
Proportion <50 c/mL at Week 24 by				Y	Y		

Endpoints	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
subgroup[3]							
Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit and Subgroup - Snapshot				Y			
Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 36/48- Snapshot, at time of Week 24 interim analysis[7,8]							
Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 36/48 using the Snapshot algorithm[1][9]							
Proportion of Subjects with Plasma HIV-1 RNA <400 & <50 copies/mL - Snapshot							
<50 c/mL by Visit				Y			
<400 c/mL at analysis timepoint (Week 24/48) outcome				Y			Y
<400 c/mL by Visit				Y	Y		
Virologic Failure endpoints							
Proportion of subjects without virologic or tolerability failure by analysis timepoint (Week 24/48) [4]	Yx2			Yx2	Yx2		Yx2
Proportion of subjects without virologic or tolerability failure by analysis timepoint (Week 36/48) [5]	Y			Y	Y		Y
Confirmed Virologic Withdrawal Criteria by Visit				Yx2[6]			Y
Viral load for Confirmed Virologic Withdrawal Criteria				Y			
Time to viral suppression (HIV-1 RNA <50 c/mL)	Y	Y		Y			
Proportion of Subjects With Detectable Viral Load Below the Limit of Quantification at				Yx2[7]			

Endpoints	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Week 24/48							
Disease Progression							
HIV Conditions including Recurrences				Y			Y
HIV Conditions excluding Recurrences				Y			
HIV Disease Progressions				Y			
Exploratory Analysis							
Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm – Projected estimate	Y[8]			Y[2]			

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. See full description in Section 11.13.
2. Study outcomes (i.e., response below 50 c/mL, virologic failure or reason for no data in the window) based on the snapshot algorithm will be summarised and listed.
3. Baseline demography (age, gender, race, country, CDC), HIV-1 subtype, Baseline CD4+ and Baseline viral load, background ART (ABC+3TC vs not ABC+3TC).
4. Outputs will be produced for TRD=F and ERD=F.
5. Outputs will be produced for TRD=F only using the MITT-E-36 & MITT-E-48 populations
6. The proportion of subjects with Confirmed Virologic Withdrawal Criteria will be summarised by visit, and also cumulatively by visit in terms of virologic non-response, virologic rebound and overall (see Appendix 6.)
7. Repeat by Baseline Viral Load
8. This summary will be produced for the week 24 study report
9. Based on the MITT-E-36 and MITT-E-48 populations

Endpoint	**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
Immunologic														
CD4+ cell counts				N			Y				Y	Y		
Plasma HIV-1 RNA Over Time														
Observed				N		Y	Yx 4[1] [2]				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. Include the interpretation of whether the virus is detected or not ('Detected' or 'Not Detected') by the assay.

2. A Separate listing for Subjects with Virologic Failure (during randomised phase and separately during the continuation phase) or Last On-treatment VL >400 c/mL. Another listing of HIV-1 RNA and CD4 at baseline versus suspected and confirmed virologic failure.

8.1.2. Planned Efficacy Statistical Analyses

Statistical Analyses
Endpoint(s)
• Proportion of subjects without virologic (ERDF) or virological and tolerability (TRDF) failure by analysis timepoint (Week 24/48)
Model Specification/Analysis Methodology
• Estimated using the Kaplan-Meier nonparametric method based on the time to Confirmed Virologic Withdrawal Criteria (CVWC) or treatment related/efficacy related discontinuation (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy) • Subjects who have not met CVW criteria and are ongoing in the study, or who have discontinued for reasons other than those related to treatment, or switch from LPV/RTV to DTG, will be censored. • 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 criteria and not discontinued due to treatment related/efficacy related reasons at the time of analysis (Week 24/48) will be presented by treatment group, along with estimated difference in proportions between treatment groups and its associated two-sided 95% CI.   ○
Model Results Presentation

• Kaplan-Meier Plots for Time to Failure will be provided. The statistical analysis table will present:
  • Number and percentage of subjects with event or censored at week 24/36/48
  • Kaplan-Meier point estimate and 95% confidence intervals at week 24/36/48
  • Kaplan-Meier point estimate and 95% confidence interval of difference between groups at week 24/48

Statistical Analyses
Endpoint(s)
• The time to viral suppression (i.e. first viral load value <50 copies/mL)
Model Specification/Analysis Methodology

• Culmulative incidence curves estimated using the Kaplan-Meier method
  ○ Subjects who withdraw for any reason or switch from LPV/RTV to DTG without having suppressed prior to the analysis will be censored
  ○ Quartiles of time to viral suppression (including median) will be summarised by treatment group. CIs will estimated using the Brookmeyer Crowley Method.
  ○ Proportion of subjects with suppression at week 24/48 presented by treatment group.
• The generalised Wilcoxon procedure will be used to estimate a p-value for detecting a difference in cumulative incidence curves between treatment groups.
  ○ Note: In general, the logrank test tends to be sensitive to distributional differences

Statistical Analyses
which are most evident late in time. In comparison, the generalised Wilcoxon test tends to be more powerful in detecting differences early in time (when the proportional hazard assumption are not met). • Cox proportional hazards model will also be used to estimate the hazard ratio (DTG vs. LPV/RTV) and 95% confidence interval. • Kaplan-Meier Plots for time to viral suppression will be provided
Model Results Presentation

• Kaplan-Meier Plots for Time to Viral Suppression will be provided.
  • The statistical analysis table will present:
  ○ Number and percentage of subjects with event or censored at week 24/48
  ○ Quartiles of time to viral suppression (including median) and 95% confidence intervals
  ○ Proportion of subjects with suppression at week 24/48
• Hazard ratio for viral suppression (DTG vs. LPV/RTV) and 95% confidence interval

Exploratory Statistical Analyses
The proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm will be estimated using the data collected at time of the Week 24 interim analysis. The purpose of this exploratory analysis is to explore the application of multiple imputation in predicting Week 48 response which may be useful for IDMC and futility analyses purposes in future. Subject data within the database at time of the Week 24 analysis should be considered into 3 groups: [1] Subjects completed the study at Week 52 [2] Subjects withdrawn from the study prior to the Week 24 data cut-off [3] Subjects ongoing within the study at time of the Week 24 data cut-off • Data for subjects in group 3 will be imputed using the methodology proposed below using all subject data from groups 1-3.
Endpoint(s)
• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm – Projected Estimate
Covariates
• Baseline Plasma HIV-1 RNA (≤ vs. >100,000 c/mL) Baseline Number of Fully Active NRTIs in the Background Regimen (2 vs.<2)
Model Specification/Analysis Methodology

• Select Log(HIV-1 RNA) samples
  • Using Markov Chain Monte Carlo methods, simulate 100 datasets replacing BLQ with values with those from a Log(Uniform(0, BLQ) distribution. The BLQ value used for this step should be slightly below the actual BLQ cut-off so that response is correctly attributed when applying the snapshot algorithm later.
  • The statistical model used for the MI data generation will be the Markov Chain Monte Carlo (MCMC) method with for the data (covariates, randomised treatment group, and Log HIV-1 RNA at Baseline, Week 4, Week 8, Week 16, Week 24, Week 36, and Week 48) to produce a monotone pattern first, and then the imputation will continue using the Regression with Predictive Mean Matching (REGPMM) method for the monotone pattern

Statistical Analyses
with the same set of covariates. ○ A seed of 200304 will be used in the SAS program. ○ One imputation is required for each of the monotone and mean matching steps ○ For subjects that discontinued from the study prior to Week 24 data cut off, replace the imputed data with their original data. Data related to these subjects will be used only for the imputation of data for those that were ongoing at time of the Week 24 data cut off. ○ Week 52 HIV-1 RNA data for subjects that completed the study will not be included in the multiple imputation. Instead, the Week 52 data will be merged back onto the imputed datasets prior to the application of the snapshot algorithm. • Using Snapshot Algorithm, derive virologic response or failure at Week 48 using snapshot algorithm, as per Section 11.13, for each imputed dataset. • For each imputed dataset, the endpoint will be analysed using a stratified analysis with Cochran-Mantel-Haenszel (CMH) weights, adjusting for Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and number of fully active background NRTIs in the background regimen (<2 vs. 2) at Baseline. This will be the same model as used for the primary endpoint. • Wilson-Hilferty transformation will be applied to normalise the CMH statistic • PROC MIANALYZE in SAS will be used to combine the 1,000 estimated proportion of subjects with plasma HIV-1 RNA <50 c/mL and difference in proportions to produce one estimate with 95% CI and associated p-value for the adjusted difference between each treatment group at Week 48
Model Results Presentation
Adjusted CMH estimate of the difference in the proportion of responders between each treatment group (DTG – LPV/RTV) and corresponding 95% confidence interval

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population, presented by treatment group with a total column and included in all reporting efforts unless otherwise specified.

The observed case (OC) dataset will be used, which contains the data that is available at a particular timepoint, with no imputation for missing values, unless otherwise stated. All displays are for the randomised phase only, unless specified otherwise. This means that the analysis other than "by-visit" summaries will not be windowed at Week 24 (AEs, maximum post-baseline toxicities). In other words, all data collected up to the point of DBF will be included in summary statistics, which could be past week 24 for subjects enrolled early in the study. However, at the Week 48 analysis, summary statistics will include data up to Week 52 for both arms.

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

For the purposes of summarising AE data, unless stated otherwise, the summaries will include post-baseline data from the Randomised Phase of the study. AEs are considered post-baseline if the onset date is on or after IP start date and before entering continuation phase. AE onset during the Continuation Phase will not be included in the Randomised Phase summaries unless it is specified in the title ie Randomised and Continuation Phase.

Following the IDMC recommendation to switch subjects on the LPV/RTV treatment arm to a regimen with DTG as the third drug, in the Week 48 analysis, the summaries of AE and laboratory data will only include AEs/laboratory data prior to switch, and AEs/labs post switch will just be listed

An issue was identified with the creatinine testing at the central laboratory. Sensitivity analyses will be conducted excluding any suspect creatinine samples from laboratory summaries including creatinine see Appendix 14.

Table 7 Overview of Planned Safety Analyses

Endpoint	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
Exposure														
Extent of Exposure				Yx 2[9]			Y[10]							
Adverse Events [19]														
Grade 2 or greater Drug-Related Diarrhoea	Y													
All AEs by SOC [1]				Y			Y (x3)							

Endpoint	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
							[11]							
All AEs by SOC by Toxicity Grade [12]				Y										
Common AEs by frequency[13]				Y	Y [15]									
Common grade 2-4 AEs by frequency [13]				Y										
All Grade 2-4 AEs by SOC				Y										
All Drug-Related AEs by SOC and toxicities [12]				Y										
All Drug-Related AEs by SOC[12]				Y										
Common Grade 2-4 Drug-Related AEs by frequency [13]				Y										
All Grade 2-4 Drug-Related AEs by SOC				Y										
Serious AEs				Y[10]			Y							
Reason for Considering as a Serious Adverse Event (FDA)							Y							
Drug-Related Serious AEs				Y										
Fatal AEs							Y							
Non-Fatal Serious AEs				Y			Y							
AEs leading to withdrawal				Y			Y							
Common non-serious AEs (FDAAA)				Y										
Number of occurrences on Non-serious AEs by SOC (EudraCT)				Y										
Number of occurrences of SAEs, Drug-related SAEs, Fatal AEs, and Drug-				Y										

Endpoint	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
related SAEs (EudraCT)														
Non-serious AEs and SAE of Mexican Subjects[8]							Y							
SAEs of non-Mexican subjects (include drug-related as a column) [8]							Y							
CV events							Y							
PSRAE							Y							
Summary of Cumulative Adverse Events				Y										
Laboratory Values														
Fasting LDL Cholesterol								Yx 3	Y					
Fasting TC/HDL ratio								Yx 3	Y					
Fasting LDL Cholesterol Treatment Emergent Abnormalities of Grade 2 or Greater[7]								Y[7]						
Clinical Chemistry							Y[3]				Yx 3[2, 3]			
Hematology							Yx 2[4]				Yx 2[2]			
Urinalysis (Dipstick)							Y							
Liver chemistries[7][6]												Y	Y	
NCEP shifts in lipids [21][7]											Yx 4	Yx 4		
ECGs[5]														
ECG Findings							Y							
Vital Signs														
Vitals Values							Y				Y			
Other														
Abacavir HSR							Y [16]							
Liver Assessment							Y [17]							
Hepatobiliary Abnormality criteria –				Y			Y							

Endpoint	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
post baseline emergent														
Columbia suicidality				Y			Y [18]							
Subjects who became Pregnant							Y							
Patient profiles							Yx 2 [20]							

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 will include subject's numbers for individual AE's & AE system organ classes, preferred terms and verbatim text.
2. Chemistry & haematology summaries will include both changes from baseline & maximum post baseline emergent toxicities. Change from Baseline chemistry summaries will be repeated for Lipids and Glucose in Conventional Units.
3. Clinical chemistry summaries will be re-run excluding subjects with suspect creatinine samples.
4. Listing of Chemistry, haematology data for subjects with abnormalities of PCI will be listed.
5. Only measured as part of CV assessment
6. Scatter Plot of Maximum vs. Baseline for ALT, Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin
7. Maximum Post-baseline
8. Includes Continuation Phase and is only for the End of Study reporting effort.
9. One for Randomisation Phase and one including the Continuation Phase.
10. Repeated for Mexican subjects. Outputs for Mexican subjects include Continuation Phase and are only needed for the end of study reporting effort.
11. 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.
12. For AEs reported more than once by a subject, the most severe intensity will be included.
13. Common AEs are those with >5% incidence in either treatment group summarised by frequency.
14. Common AE by frequency graph description
15. Plots of incidence rates and relative risk for DTG vs. LPV/RTV.
16. Separate listings for exposure to abacavir, history of drug allergies, family conditions, skin rash, symptoms, vital signs, individual symptoms and diagnostic category assignment.
17. Separate listings for time of event from trt, RUCAM score, biopsy, imaging, past/ current conditions & FU
18. Listing but classed as a Table. Includes Baseline and lists all visits for a subject who reports any ideation or behaviour at any visit..
19. Adverse events will be coded using the MedDRA coding dictionary to give a preferred term and a system organ class. Summaries include only Post-baseline AEs with onset date up to cut-off date for reporting effort, listings include all AEs including those with onset pre- or post-treatment.
20. Patient profiles for subjects meeting protocol defined liver stopping criteria and for patients with virological failures. Patient profiles can also be provided for any other subjects, as necessary for medical review.
21. One output will be created for each lipid parameter. Bar chart for LDL, HDL, TC, Trig and HDL/TC ratio

8.2.2. Planned Safety Statistical Analyses

Statistical Analyses
Endpoints
• Change from Baseline in fasting LDL cholesterol at Weeks 24 and 48 • Change from Baseline in fasting TC/HDL ratio at Weeks 24 and 48
Lipids Last Observation Carried Forward (LOCF) Dataset
• See Appendix 7
Covariates
• Baseline Plasma HIV-1 RNA (≤ vs. >100,000 c/mL) • Baseline Number of Fully Active NRTIs in the Background Regimen (2 vs.<2)   • Age (<35, 35-<50, ≥50)
Data Handling
• If a subject is on lipid-lowering therapy from Baseline, they will be excluded from the analysis. • If a subject initiates lipid-lowering therapy during the study, all visits after that date will be set to missing. • All other data remains as is (observed or missing). • A multiple imputation technique will be used to deal with the missing data.
Model Specification
• Multiple imputations will be drawn from a multivariate normal model for the data (Fasted LDL, cholesterol and fasted TC/HDL measurements at Baseline, Week 16, Week 24 and Week 48 (including covariates) with a Markov Chain Monte Carlo (MCMC) approach used to estimate posterior distributions. A seed of 200304 will be used in the SAS program. Where a subject has a monotone or non-monotone pattern of missingness, all of their missing observations can be imputed under this approach. The absolute value will be imputed before the change value is calculatedImputations will be drawn separately for subsets of subjects according to their treatment group, i.e., based on means and variance-covariances from the same treatment group (Missing At Random (MAR) approach) conditioning on observed covariates listed above. This will be known as the MAR method. • The imputations will be carried out 1,000 times. An ANOVA will be performed on each datasets produced adjusting for treatment, baseline value and the categorical covariates, regardless of their significance. PROC MIANALYZE in SAS will be used to combine the 1,000 estimated means and difference to produce one estimated mean with 95% CI and associated p-value for the adjusted mean difference between each treatment group at Week 24/48. • Interactions between treatment and each of the covariates will not be assessed.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted means and corresponding standard error of means (SEs) will be presented for each treatment, together with estimated treatment difference (DTG – LPV/RTV) and corresponding 95% confidence interval and p-value. • Plots of LS means and 95% confidence intervals from the model will be generated for each treatment by time.

Statistical Analyses
Sensitivity Analyses
Sensitivity analyses will be performed as follows: • using the standard Observed Case (OC) dataset, with no adjustment or imputation for withdrawing, initiating lipid-lowering agents or other missing data. An analysis of covariance (ANCOVA) model will be used with covariates (listed above), and baseline value as a covariate. • using the Lipid LOCF dataset, but also carrying forward the last observation to any missing visits, an ANCOVA model will be used with treatment, covariates (listed above), and baseline value as a covariate.

Statistical Analyses
Endpoints
• The incidence of maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24 and 48 • The incidence of maximum post-Baseline emergent Grade 2 or greater drug-related diarrhoea by Weeks 24 and 48
Dataset
• The observed case (OC) dataset uses only the data that is available at a particular timepoint, with no imputation for missing values.
Model Specification/Analysis Methodology
• Endpoints will be statistically analysed for the comparison between DTG and LPV/RTV by Fisher's exact test using the Safety Population
Model Results Presentation
• Incidence for each treatment group and a p-value for the difference in incidence between treatment groups.

9. OTHER STATISTICAL ANALYSES

9.1. Health Outcomes Analyses

9.1.1. Overview of Planned Analyses

The Health Outcomes (HO) analyses will be based on the Intent-to-treat Exposed population, presented by treatment group with a total column and included in all reporting efforts unless otherwise specified.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 17: List of Data Displays.

Following the IDMC recommendation to switch subjects on the LPV/RTV treatment arm to a regimen with DTG as the third drug, the Week 48 summaries and analyses of HO data will only include HO data prior to switch, and HO post switch will just be listed.

Table 8 Overview of Planned Health Outcome Analyses

Endpoint	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
HIVTSQs														
Individual Item Scores				Y			Y				Y			
Treatment Satisfaction Score				Y			Y	Y x2			Y			
HIVTSQc														
Individual Item Scores (Change)	Y[1]			Y			Y							
Treatment Satisfaction (Change)	Y			Y			Y							
MMAS-8														
Total Score				Y			Y							
Adherence Level	Y			Y			Y							
Gastrointestinal Symptom Rating Scale (GSRS)														
Individual Item Scores				Y			Y							
Diarrhoea Syndrome Score				Y			Y	Y			Y			
Indigestion Syndrome Score				Y			Y	Y			Y			
Constipation Score				Y			Y	Y			Y			
Abdominal Score				Y			Y	Y			Y			
Reflux Score				Y			Y	Y			Y			

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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.
- HIVTSQ questionnaire included in Section 11.6.6
  Individual = Represents FL related to any displays of individual subject observed raw data
  [1] Item 12 only

9.1.2. Planned Health Outcomes Statistical Analyses

Statistical Analyses
HIVTSQs
• Change from Baseline at Week 4, Week 24, and Week 48: ○ **Treatment Satisfaction Score**
Model Specification
• The MMRM will adjust for visit, Baseline Plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and Baseline Number of Fully Active NRTIs in the Background Regimen (2 vs.<2). • The model will make no further assumptions about the correlations between a subject's score (the correlation matrix for within-subject errors will be unstructured). • The repeated measures analysis will assume that the treatment difference can vary between visits (ie. a treatment*visit interaction will be included in the model), and separates estimates and 95% confidence intervals will be produced at each visit. The model will also assume that the effect of baseline score can vary between visits (ie. baseline score*visit interactions will be included in the model). • Interactions between treatment and each of the covariates will not be assessed unless the exploratory subgroup analyses described in Section 7.1.2 on the primary endpoint highlights significant interactions. In this situation, the interaction(s) of interest will be assessed and, if necessary, results will be reported in the clinical study report. Interactions between treatment and the baseline score will be investigated but not included in the model. If interactions are found to be significant, results might have to be presented separately by subgroup.
Dataset
• The observed case (OC) dataset uses only the data that is available at a particular timepoint, with no imputation for missing values in addition to the ones described in Section 11.6.7.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The summaries will include the adjusted mean change from baseline and confidence interval for each treatment group across visits. • The interaction between treatment and the baseline score will be included in a footnote.

Statistical Analyses
HIVTSQc
• **Treatment Satisfaction Score (Change) at Week 48**
Model Specification
• An analysis of covariance (ANCOVA) model will be used with covariates: treatment, Baseline Plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and Baseline Number of Fully Active NRTIs in the

Statistical Analyses
Background Regimen (2 vs.<2).
Dataset
• The observed case (OC) dataset uses only the data that is available at a particular timepoint, with no imputation for missing values in addition to the ones described in Section 11.6.7.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted means and corresponding standard error of means (SEs) will be presented for each treatment, together with estimated treatment difference (DTG – LPV/RTV) and corresponding 95% confidence interval and p-value.

Statistical Analyses
MMAS-8
• Adherence level
Model Specification/Analysis Methodology
• Endpoints will be statistically analyzed for the comparison between DTG and LPV/RTV by Fisher's exact test using the ITT(e) Population
Dataset
• The observed case (OC) dataset uses only the data that is available at a particular timepoint, with no imputation for missing values in addition to the ones described in Section 11.6.7.
Model Results Presentation
• Incidence for each treatment group and a p-value for the difference in incidence between treatment groups.

Statistical Analyses
Gastrointestinal Symptom Rating Scale (GSRS)
• Change from Baseline at Week 4, Week 24, and Week 48: ○ Diarrhoea Syndrome Score ○ Indigestion Syndrome Score ○ Constipation Score ○ Abdominal Score ○ Reflux Score
Model Specification
• A Wilcoxon rank sum test will be used to compare the change in gastrointestinal symptom rating score sub-items for subjects treated with DTG and LPV/RTV at each visit

Statistical Analyses
Dataset
• The observed case (OC) dataset uses only the data that is available at a particular timepoint, with no imputation for missing values in addition to the ones described in Section 11.6.7.
Model Results Presentation
• Change from baseline will be presented and the p-value from the Wilcoxon rank sum test will be presented to compare the change from baseline between the two treatment groups.

9.2. Virology Analyses

9.2.1. Overview of Planned Analyses

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

Phenotype data may not be available for all subjects in China at the time of the Week 24 analyses. The China subjects may also have genotype data from Q2 and/or Monogram. In the event that subjects have both Q2 and Monogram data at a timepoint, the Monogram data will be used. Footnotes will be included in summaries indicating which subjects have Q2 data only or Q2 and Monogram.

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 17 List of Data Displays.

Table 9 Overview of Planned Virology Analyses

Endpoint	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Incidence of treatment-emergent genotypic and phenotypic resistance to DTG, LPV/RTV and other on-study ART in subjects meeting confirmed virologic withdrawal criteria							
Genotype							
Summary of Genotypes Available				Y			
Treatment Emergent Major Mutations of NRTI, NNRTI and PI Classes				Y			
Pre-specified Treatment Emergent IN Substitutions at Time of Confirmed Virologic Withdrawal				Y			

Endpoint	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Changes in Genotypic Susceptibility (GSS) to Background ART Therapy at Time of Confirmed Virologic Withdrawal				Y			
All Genotypic Data							Y
Phenotype							
Summary of Phenotypes Available				Y			
Fold Change to DTG and LPV/RTV at Baseline and Time of Confirmed Virologic Withdrawal				Y			
Changes in Phenotypic Resistance (PSS_f) to Background ART Regimen at Time of Confirmed Virologic Withdrawal				Y			
All Phenotypic Data							Yx2[2]
Net Assessment for Overall Susceptibility Score							
Overall Susceptibility Score (OSS)				**Y**[3]			
Other							
Key Virologic Data							Yx4[1]
Virology Data at Confirmed Virologic Withdrawal				**Y**			

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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. A Separate listing for Subjects with Virologic Failure (during randomisation phase and separately during the continuation phase) or Last On-treatment VL >400 c/mL.
2. Include a separate listing for screening results from Quest.
3. Produce for CVW resistance populations.
4. This is a listing of subject data to be included as a Table.

10. REFERENCES

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11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Time and Events
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Treatment States & Phases
Section 11.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Virology
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Section 11.8	Appendix 8: Values of Potential Clinical Importance
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Section 11.13	Appendix 13: Snapshot
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Section 11.16	Appendix 16: Example SAS code for Additional Estimand 2
Section 11.17	Appendix 17: List of Data Displays

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

11.1.1. Exclusions from Per Protocol Population

Protocol deviations leading to exclusion from PP population are those deviations which

- may directly impact the efficacy endpoint of HIV-1 RNA; or
- lead to permanent discontinuation of IP/withdrawal and hence indirectly impact the efficacy endpoint by causing data to be missing.

The following criteria define the protocol deviations which, if they occur prior to an analysis timepoint of interest, will lead to exclusion of a subject from the Per-Protocol population for that analysis. Potential protocol deviations leading to exclusion from PP population will be reviewed by the study team to confirm that they meet these criteria. This review will occur before the clinical database has been frozen for analysis.

A subject meeting any of the following criteria prior to the timepoint of interest (eg week 24 or 48) will be excluded from the Per Protocol population for the week 24 interim or week 48 respectively:

Number	Exclusion Description
01	Subject deviates from any inclusion or exclusion criteria, as recorded in the eCRF

02	Prohibited medications.
	
	There are several sub-categories for prohibited medication use:
	
	a) Subject receiving prohibited non-ART medications (See protocol) or receiving non-ART medication that would potentially impact exposure or response to therapy. Duration of >2 consecutive weeks will be considered prohibited.
	
	• HIV immunotherapeutic vaccines
	• Other experimental agents
	• Antiretroviral drugs not otherwise specified in the protocol
	• Cytotoxic chemotherapy
	• Radiation therapy
	• Immunomodulators:
	  • Calcineurin Inhibitors
	  • Cyclosporine A, Pimecrolimus, Tacrolimus
	  • Fluorouracil (including topical)
	  • Interferon (rectal and transdermal routes are permitted)
	• mTor Kinase Inhibitors

Number	Exclusion Description

	• Everolimus, Sirolimus
	• Methotrexate
	• Purine Analogues
	  • Azathioprine, 6-Mercaptopurine
	• Targeted Immune Modulators (Biological Response Modifiers)
	  • Abatacept, Adalimumab, Alefacept, Anakinra, Certolizumab, Efalizumab, Etanercept, Golimumab, Infliximab, Natalizumab, Rituximab, Tocilizumab, Ustekinumab
	• HCV therapy
	sofosbuvir (Sovaldi, Virunon),ledipasvir/sofosbuvir (Harvoni), paritaprevir/ritonavir/ombitasvir + dasabuvir (Viekira Pak),paritaprevir/ritonavir/ombitasvir (Viekirax), dasabuvir (Exviera), simeprevir (Olysio), telaprevir (Incivek, Incivo), boceprevir (Victrelis), peginterferon alfa (e.g. Pegasys), interferon alfa (e.g. Intron A, Roferon-A), ribavirin (Copegus, Rebetol)
	
	b) Chronic use (>30 days) of systemic glucocorticoids
	• oral & iv routes are not permitted
	• topical & nasal routes are permitted
	
	c) Treatment dependent prohibited medications.
	Any duration is considered prohibited..
	
	For subjects randomised to DTG:
	• Carbamazepine
	• Dofetilide
	• Oxcarbamazepine
	• Phenobarbital
	• Phenytoin
	• Pilsicainide
	• Rifampicin
	• rifapentine
	• St. John's wort (Hypericum perforatum
	
	For subjects randomised to LPV/RTV:
	• Alfuzosin
	• Amiodarone
	• Antihistamines (astemizole, terfenadine)
	• Cisapride
	• Ergot alkaloids (dihydroergotamine, ergonovine, ergotamine, methylergonovine)
	• Fusidic acid (in dermatological infections)
	• HMG Co-A reductase inhibitors (specifically lovastatin, simvastatin)

Number	Exclusion Description
	• Pimozide • Rifampicin • Sildenafil (when used for the treatment of pulmonary arterial hypertension) • Vardenafil • Avanafil • Midazolam (oral) • Triazolam • St John's wort (Hypericum perforatum) As these deviations are treatment dependent it will not be possible to identify if they are deviations until treatment details are known post unblinding. d) **Prohibited ART Medication Use** Receiving ART medication other than that prescribed/allowed by the study for any duration
03	Non-permitted switch of background ART, specifically: On-treatment changes of background ART post the Week 4 visit window that • Are made for reasons other than toxicity or tolerability management, or • Introduce new agents which are not within class substitutions, or Result in a background regimen that consists of more than 2 NRTIs (or 3 NRTIs in the case of subjects receiving 3TC/FTC for treatment of hepatitis B. If a subject does not take an NRTI or a fully active NRTI this will be considered a protocol deviation and lead to exclusion from the PP Population. This will be considered as a non-permitted switch of background ART.
04	Subject took/received incorrect IP, i.e., other than the one to which they were randomised for greater than 10% of the total time On-treatment. It will not be possible to identify whether subjects received a different treatment to the one they were randomised to until post unblinding.
05	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. This is mentioned in the PDMP but it is not listed as a PD category.
06	Permanent discontinuation of IP/withdrawal due to a reason of "Protocol Deviation" (as recorded in the eCRF). This is stated in the PDMP but it is not listed as a PD category as the PD will be classified under one of the other PD categories.

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

Procedures			Randomised Phase							Continuation Phase[b]		Withdrawal	Follow-up[c]
	Screening[a]	Baseline (Day 1)	Day 1 to Week 48						4-week Treatment Extension				
			Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 52	Week 60	Every 12 weeks thereafter		
Clinical and Other Assessments													
Written informed consent	X												
Inclusion/Exclusion criteria[d]	X												
Subject demography	X												
Medical history[e]	X												
Prior ART history	X												
CDC HIV-1 classification	X	X											
Limited physical examination/	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height		X											
Current medical conditions		X											
CV risk assessment[g]		X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures			Randomised Phase							Continuation Phase[b]		Withdrawal	Follow-up[c]
	Screening[a]	Baseline (Day 1)	Day 1 to Week 48						4-week Treatment Extension				
			Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 52	Week 60	Every 12 weeks thereafter		
HIV associated conditions			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	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
SAEs	X[i]	X	X	X	X	X	X	X	X	X	X	X	X
GSRS		X	X			X		X				X	
HIVTSQs		X	X			X		X				X	
HIVTSQc								X				X	
MMAS-8		X	X			X		X				X	
Laboratory Assessments													
Quantitative plasma HIV-1 RNA PCR	X	X	X	X	X	X	X	X	X[j]	X	X	X	
Lymphocyte subset	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma for HIV genotyping	X												
Plasma for storage[k]	X	X	X	X	X	X	X	X	X	X	X	X	
HLA-B* 5701 testing[l]	X												
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/INR	X												
Fasting lipids and glucose[m]		X			X	X		X					
Pregnancy test[n]	S	U	S	S	S	S	S	S	S	S	S	S	S

Procedures			Randomised Phase							Continuation Phase[b]		Withdrawal	Follow-up[c]
	Screening[a]	Baseline (Day 1)	Day 1 to Week 48						4-week Treatment Extension				
			Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 52	Week 60	Every 12 weeks thereafter		
HBsAg, anti-HBc and anti-HCV[o]	X												
HBV DNA[p]		X											
Pharmacogenetic sample[q]		X											
PBMCs[r]		X											
Investigational product													
IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP		X	X	X	X	X	X	X	X[s]	X	X		
IP accountability (pill counts)			X	X	X	X	X	X	X	X	X	X	

a. The 28-day Screening period may be extended to 42 days. Randomisation may occur as soon as all Screening results are available.
b. For subjects who completed randomised DTG through Week 52 and entered into the DTG Continuation Phase: subjects completing the DTG Continuation Phase must return to the clinic when transitioning to commercial supplies. Conduct study assessments, with the exception of dispensing IP, as specified for all Continuation Phase visits at this end of Continuation Phase visit.
c. A follow-up visit will be conducted 4 weeks after the last dose of study provided IP and is required only if a subject has ongoing AEs or laboratory abnormalities at the last on-study visit. The assessments performed should reflect what is considered medically necessary to assess the event(s).
d. Inclusion/exclusion criteria will be fully assessed at the Screening visit. Changes between the screening visit and the Day 1 visit should be assessed to ensure eligibility, including additional assessments performed at Day 1.
e. Full medical history will be collected. Targeted Medical History assessments will include cardiovascular, gastrointestinal (e.g. GI bleeding, PUD, etc), metabolic (e.g. Type I or II DM), psychiatric (e.g. depression), renal (e.g. nephrolithiasis, nephropathy, renal failure) and neurological disorders.
f. Limited physical examination to include blood pressure at Baseline (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
g. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
h. On Day 1, the Columbia Suicidality Severity Rating Scale is to be administered prior to randomisation.
i. Only SAEs related to study participation or to a concomitantly administered GSK/ViiV product will be collected between obtaining informed consent and administration of IP at Day 1.
j. At Week 52, repeat HIV-1 RNA testing will only be performed for subjects with HIV-1 RNA ≥50 c/mL at Week 48.

k. Plasma samples for storage will be collected at each visit for possible future analyses (including but not limited to HIV-1 RNA genotypic and phenotypic analyses, HIV-1 RNA levels, and immunological parameters). These samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable. Additionally, for genotypic and phenotypic resistance analyses Baseline samples from all subjects will be used and later samples in cases of confirmed virologic withdrawal criteria met (for paired baseline and endpoint genotypes).
l. Subjects starting ABC as one of the NRTIs should have been screened and be negative for the HLA-B*5701 allele.
m. An overnight fast is preferred, however a minimum of a 6 hour fast is acceptable.
n. Pregnancy testing will be conducted (women of child bearing potential only) on serum (S) samples with the exception of Day 1, which must be a urine (U) test to confirm status prior to administration of IP.
o. Subjects who are hepatitis B surface antigen (HBsAg) positive require appropriate HBV therapy based on local guidelines (see Section 6.2.3 for details).
p. HBV DNA testing will be performed on Day 1 for subjects with negative HBsAg and positive hepatitis B core antibody (anti-HBc) results at Screening. Subjects with positive anti-HBc and positive HBV DNA results require appropriate HBV therapy based on local guidelines (see Section 6.2.3 for details).
q. Informed consent for optional pharmacogenetics (PGx) research must be obtained before collecting a sample. Collection of the PGx sample at Day 1 is preferred; however, this sample may be collected at any time during the study.
r. Whole blood collection (please refer to the SPM).
s. For subjects receiving DTG during the Continuation Phase only.

11.3. Appendix 3: Assessment Windows

Laboratory data, vital signs, health outcomes assessments, and genotypic and phenotypic data will be assigned to assessment windows according to actual dates rather than the nominal visit labels as recorded on the eCRF or in the laboratory database. The CVW algorithm will be derived using nominal CRF visit rather than using the assessment window defined below.

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

Based on the Study Day (see Section 11.6.1), assessments are assigned as shown in Section 11.3.1.

11.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy	Snapshot (MSDF) endpoints	-28	≤-4	≤-4	Screen
		1	-3	1	Day 1
		29	2	42	Week 4
		57	43	84	Week 8
		113	85	126	Week 16
		169	127	210	Week 24
		253	211	294	Week 36
		337	295	378	Week 48
		421	379	462	Week 60
		7*w + 1	(7*w – 41)	(7*w + 42)	Week w w = 72, 84, 96,…
		Study Day of last dose + 28	> (Study Day of last dose + 1)	> (Study Day of last dose + 1)	Follow-up
Safety/Virology /Health Outcome		-28	≤-4	≤-4	Screen
		1	-3	1	Day 1
		29	2	42	Week 4
		57	43	84	Week 8
		113	85	126	Week 16
		169	127	210	Week 24
		253	211	294	Week 36

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
		337	295	350	Week 48
		365	351	392	Week 52
		421	393	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 key timepoints at Week 24 and Week 48, the efficacy windows have been defined to cover ± 6 weeks, regardless of the midpoint between adjacent target Study Days. The windows for the adjacent periods are adjusted accordingly.
- For parameters that are not scheduled to be assessed at particular visits, the all-inclusive windows defined above will still be used; however, data summaries will only report scheduled visits. 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).
- See Section 11.6.1 for how to handle multiple assessments within a time window.

11.4. Appendix 4: Treatment States and Phases

11.4.1. Study Phases

All displays are for the randomised phase only, unless specified otherwise. This means that the analysis other than "by-visit" summaries will not be windowed at Week 24 (AEs, maximum post-baseline toxicities). In other words, all data collected up to the point of DBF will be included in summary statistics, which could be past week 24 for subjects enrolled early in the study. However, at the Week 48 analysis, summary statistics for the randomised phase will only include data up to Week 52 for both arms.

For subjects entering the continuation phase, which phase an assessment or an event occurred in will be determined by comparing the event date with the week 52 visit date.

The study phases are defined as follows:

Phase	Start	End
Randomised Phase	IP start date	Week 52 DOV, IP end date or Withdrawal date if on or before Week 52 DOV
Continuation Phase	Week 52 DOV	IP end date or Withdrawal date if post Week 52 DOV

11.4.2. Treatment States

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

11.4.2.1. Treatment States for HIV-1 RNA Data, Laboratory Data, HIV Associated Conditions, Vital Signs, , Health Outcomes assessments, 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

11.4.2.2. Treatment States for AE Data

For adverse events, a partial AE start date uses imputation as described in Section 11.7.

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 [Inform/CRF OR value is missing].

NOTES:

- 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.

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

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

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

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

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

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

considered concomitant and post-treatment if they start on the IP stop date).Any ART entered on the Prior ART eCRF with partial end date will be assumed to have finished before Screening.

Table 10 Concomitant, and Post-treatment Classification of Medications

	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

11.4.3. Post-treatment Assessments and Phases

On-treatment and Post-treatment assessments and events will be classified as occurring during the Randomised Phase or the Continuation Phase of the study as follows:

- If a subject did not enter the Continuation Phase, then any Post-treatment data will be assigned to the Randomised Phase.

- For subjects who did enter the Continuation Phase, any Post-treatment data will be assigned to the Continuation Phase.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Dolutegravir 50mg once daily	DTG	1
B	Lopinavir/ritonavir 800mg/200mg once daily or 400mg/100mg twice daily	LPV/RTV	2

NOTES:

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

11.5.2. Baseline Definition & Derivations

11.5.2.1. Baseline Definitions

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

In the scenario where the treatment start date is more than 1 week after randomisation date, the randomisation date will be used as baseline for change from baseline. Therefore, for example, the week 12 visit data would be included in the week 12 visit summary rather than the week 8 visit summary. All analyses will use this rule, except for resistance analyses; as the resistance test at or just before treatment start is more representative of a patient "baseline" rather than the randomisation date, since patients would have stayed on a failing regiment for longer than they should have.

Example:

A subject was randomised on 26Feb2016 but did not start IP until 18Mar2016. Baseline will be 26Feb2016 for everything apart from resistance analyses where baseline will be 18Mar2016.

11.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

11.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software and TSCG will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: \ARPROD\GSK1349572\200304
QC Spreadsheet	: \ARPROD\GSK1349572\200304\(Week24, Week48 or Final)\Documents
Analysis Datasets	
• Analysis datasets will be created according to according to CDISC standards (SDTM IG Version 3.1.3 & AdaM IG Version 1.0. • For creation of AdaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for every reporting effort.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 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
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Actual time relative to dosing will be used in figures, summaries, statistical analyses and

Reporting Standards	

calculation of any derived parameters, unless otherwise stated.
• 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.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	

Unscheduled Visits	
• Unscheduled visits will be assigned to a study visit using the all-inclusive windows defined in Section 11.3. • However, data summaries will only report visits that are planned assessment time points for each parameter (according to the T&E table). • Assessments at unscheduled visits will be included for 'any time On-treatment' time points and in data listings, as well any algorithms that make use of additional data (e.g., Snapshot).	
Invalid Laboratory Assessments	
• Certain laboratory endpoints are required to be collected in a fasting state, i.e., glucose and lipids (triglycerides, total cholesterol, HDL, LDL). If these endpoints are collected in a non-fasting state, then the results will be excluded from summaries; such results will be included in data listings with the fasting status noted.	
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.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. Week 24 cut off date

For the week 24 interim it is necessary to define a cut-off for the purposes of defining prohibited medications and also for the calculation of total time on treatment during the Week 24 time period.

To be considered prohibited the medication has to be taken before the date of Week 24 viral load. If the date of the Week 24 viral load is before the prohibited medication was taken then this does not impact the snapshot algorithm. If the Week 24 viral load date is missing then the cut off date is defined as follows:

- For subjects who have a Week 24 visit:
  use Week 24 date from Visit dataset (SV).

- For subjects who have withdrawn (or last IP end date) before Week 24:visit
  use the minimum of : withdrawal date, disposition date, last visit date, last drug exposure date (while taking into account study drug interruptions) and last laboratory date.

- For subjects who have not withdrawn but no IP stop date or week24 visit date yet:
  Cut-off= IP start date + week24studyday - 1

  where week24studyday could be 169 (the target date of wk24 window) or 210 (upper bound of wk24 window).

The last exposure data should use both EXSTDTC and EXENDTC in case the IP was interrupted and re-started.

This cut-off date also applies for the calculation of total on treatment during Week 24.

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

11.6.2. General

Multiple Measurements at One Time Point

• If after window assignment (see Section 11.3), 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:
  • the assessment closest to the window target Study Day;
  • if there are multiple assessments equidistant from the target Study Day, then the mean of these values will be used. For HIV-1 RNA, the geometric mean of the number of copies will be used as opposed to the arithmetic mean
• Assessments not chosen for use in summary statistics by this algorithm will still appear in the associated listings. Also, such valid assessments will be used when determining values of

Multiple Measurements at One Time Point

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., MSDF or LOCF).
• In the event of laboratory re-tests being performed the last re-test in the visit window will be used. For example:
  • *If a subject had a week 24 viral load and then two re-tests (ie three viral loads labeled as week 24, unscheduled 1 unscheduled 2). and the first two viral loads were within the upper bound of the week 24 visit (Day 210) but the last re-test was slotted to week 36 then the last re-test would not be used for the week 24 snapshot.*
  • *If a subject had a week 24 viral load but the re-test was performed on Day 220 (week 36) then the re-test viral load would not be used for the week 24 snapshot.*

Study Day

• Calculated as the number of days from the initial 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 (Section 11.4.2). Post-baseline may be further specified according to phase of the study: Randomised or Continuation (Section 11.4.1).

11.6.3. Study Population

Demographics
Age

• Age, in whole years, will be calculated with respect to the subject's Screening visit.
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• 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.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**
Background ART
• For purposes of calculating susceptibility scores (Section 11.6.6), a subject's baseline background ART regimen is defined as the last full regimen received at the end of the Week 4

Demographics

visit window. This allows time to accommodate any early, protocol-permitted changes in background ART or for short, unexpected delays in implementing the chosen background NRTI regimen

WHO First Line and Second Line Regimen

First line combination regimen is defined as follows:

```
TDF + 3TC + EFV
TDF + FTC + EFV
AZT + 3TC + EFV
AZT + FTC + EFV
D4T + 3TC + EFV
D4T + FTC + EFV
AZT + 3TC + NPV
AZT + FTC + NPV
D4T + 3TC + NPV
D4T + FTC + NPV
TDF + 3TC + NVP
TDF + FTC + NVP
```

Second line combination regimen is defined as follows:

```
AZT + 3TC + LPV/r
TDF + 3TC + LPV/r
TDF + FTC + LPV/r
```

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, 2008] is**

for females:

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

for males:

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

where

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

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)**

Demographics
$I_s = \begin{cases} 1, \ current\ smoker \\ 0, \ otherwise \end{cases}$ $I_d = \begin{cases} 1, \ diabetic \\ 0, \ otherwise \end{cases}$ • A subject will be considered as treated for high blood pressure if during screening it has specified that is suffering from hypertension.   • A subject is classified as diabetic if current or past is indicated in the medical conditions eCRF for Type 1 or Type 2 diabetes mellitus, or if baseline fasting glucose ≥7.00 mmol/L (126 mg/dL).   • Smoking status is collected in the eCRF on Day 1. A current smoker is defined as currently smoking/using tobacco or has smoked/used tobacco within the previous 6 months; a former smoker is defined as previously smoked/used tobacco products and has not smoked/used tobacco products within the previous 6 months.   • This calculation will not be performed for subjects who have indicated current or past myocardial infarction conditions on the eCRF. These subjects will not be included in summary statistics of risk, but will be counted in the highest category of risk in the summary by category.

11.6.4. Safety

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1   • Subjects who were randomised but did not report a treatment start date will be categorised as having zero days of exposure.   • Missing Treatment Stop Date will be imputed, for purposes of calculating exposure, as the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.   • 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   ◦ 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%).
ECG Parameters
Not applicable as not routinely collected.

Adverse Events
AE Severity – DAIDS Grading
• The DAIDS grading for severity of clinical adverse events will be performed.   • See protocol for DAIDS grading criteria.

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

Lab Toxicities – DAIDS Grading

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

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

National Cholesterol Education Program (NCEP) Lipid Categories

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

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

Total Cholesterol / HDL Cholesterol Ratio

- When both total cholesterol and HDL cholesterol results are available from the same date for a subject, then the ratio will be calculated by dividing the total cholesterol result by the HDL cholesterol result.

Hepatitis Status
• Hepatitis C status will be determined using antibody (anti-HCV) assessments performed during screening. • A subject will be considered chronically infected with hepatitis B virus (HBV) if they test HbsAg positive OR anti-HBc positive with HBV DNA present (HBV DNA is determined at Baseline for subjects who are tested HbsAg negative and anti-HBc positive at Screening).

Other Safety Endpoints
Columbia Suicide Severity Rating Scale (C-SSRS)

• Missing data will not have any imputation performed.
• Incomplete calls:
  ◦ when no complete call is databased on the same day, the incomplete data will be used
  ◦ 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, the latest entry will be used.
  ◦ If they occur on different days, take the entry closest to the target visit date.

11.6.5. Efficacy

Efficacy
Snapshot (Missing, Switch or Discontinuation=Failure)

• The FDA's "snapshot" algorithm is also known as the MSDF algorithm. 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 11.3) 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.
• A subject may also be considered a Virologic Failure if they make changes to their background regimen. This includes:
  ○ background ART substitutions not permitted per protocol;
  ○ background ART substitutions permitted per protocol unless the decision to switch is documented as being before or at the first On-treatment visit where HIV-1 RNA is assessed.

Efficacy

- For each scheduled assessment time, the MSDF (also known as snapshot) response rate for a given threshold (e.g., <50 c/mL) is defined as:

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

- Full details of the algorithm, including the handling of special cases, are included in Section 11.13.

Treatment and Efficacy Related Discontinuation = Failure (TRDF and ERDF)

- The analysis of time to confirmed virologic withdrawal criteria (CVWC) or discontinuation due to treatment related reasons (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy) will censor subjects who have not met CVW criteria and are ongoing in the study, or who have discontinued for reasons other than those related to treatment. This will be the Treatment Related Discontinuation = Failure (TRDF) data.
- Subjects who have not met CVW criteria and are ongoing in the study, or who have discontinued for reasons other than lack of efficacy, will be censored in the analysis of the Efficacy Related Discontinuation = Failure (ERDF) data.

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.

Variance Estimator of Cochran Mantel-Haenszel Risk Difference

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

where

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

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

CVW Derivation

There are 3 parts to the derivation of CVW. All parts of the derivation need to use nominal visits (i.e. VISIT and VISITNUM).

Virologic Non-response (Parts 1 &2)

- A decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥400 c/mL on or after Week 24.

Virologic Rebound (Part 3)

- Confirmed rebound in plasma HIV-1 RNA levels to ≥400 c/mL after prior confirmed suppression to <400 c/mL.

A patient can only be classified as CVW for the analyses if the patient is on-treatment at the time of the HIV-RNA value.

Part 1. A decrease in Plasma HIV-1 RNA of less than 1 log10 c/mL by week 16, with subsequent confirmation, unless Plasma HIV-1 RNA is <400 c/mL

- This applies to Week 16 data only (where INT(VISITNUM)=80)
- If there is a decrease < 1 log10 from Baseline at Week 16 and LBORRESN>=400, then -> suspected virologic withdrawal
- If there is a confirmatory sample, then check if there is a decrease <1 log10 from Baseline and the LBORRESN>=400 then confirmed virologic withdrawal
- The protocol states that the confirmatory sample needs to be taken within 1-4 weeks of initial sample, unless one of the extenuating circumstances outlined below apply:

The following guidelines will be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the subject should receive full dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunisation, during which time the subject should receive full dose of IP.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of IP.
- The subject should have received full doses of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done.

Example: subject

subject	nominal visit	visit date	c/mL	log10 c/mL	log10 decrease from BL	CV outcome	comments
	Baseline	16-Feb-15	3398	3.53			
	Week 4	16-Mar-15	39	1.59	1.94		
	Week 8	13-Apr-15	2354	3.37	0.16		
	Week 16	08-Jun-15	368742	5.56	-2.03	Suspected virologic withdrawal	<1 log 10 decrease from baseline, and value >400 c/mL
	Week 16	18-Jun-15	17293	4.24	-0.71	Confirmed virologic withdrawal	<1 log 10 decrease from baseline, and value >400 c/mL

Example subject

subject	nominal visit	visit date	c/mL	log10 c/mL	log10 decrease from BL	CV outcome	comments
	Baseline	28-Mar-15	38286	4.58			
	Week 4	25-Apr-15	332	2.52	2.06		
	Week 8	22-May-15	66	1.82	2.76		
	Week 16	18-Jul-15	<50	<1.70	2.99		
	Week 24	12-Sep-15	87394	4.94	-0.36	suspected virologic withdrawal	value >400 on/after week 24
	Week 24	06-Oct-15	413	2.62	1.97	confirmed virologic withdrawal	Consecutive value >400 on/after week 24

Part 2: Confirmed Plasma HIV-1 RNA levels >=400 c/mL on or after Week 24

- If patient is not already a confirmed VF due to the rules in Part 1, we can then continue to check the results from Week 24 onwards
- Use nominal visits i.e. int(visitnum)>=100
- If a patient has a sample on/after Week 24 and the result is >=400 then -> suspected virologic withdrawal.
- If a patient then has a 2nd consecutive sample >=400 then -> confirmed virologic withdrawal.

Part 3: Confirmed rebound in plasma HIV-1 RNA levels to >=400 c/mL after prior confirmed suppression to <400 c/mL

- Virologic rebound can happen at any visit.
- Patient must have 2 consecutive values <400, followed by 2 consecutive values >=400.
- Once a patient has 2 consecutive values <400, if the next value is >=400 this is a suspected rebound
- If a patient then has a 2nd consecutive sample >=400 then this is a confirmed rebound
- Subject (above) is classified as virologic rebound, as they have values <400 at Weeks 4, 8, and 16, then continues to have 2 consecutive values >=400. On 06Oct2015, the subject is a 'confirmed rebound'. Also see subject below:

Note that there is greater than 1-4 weeks (23Jul-26Aug) from suspected sample to confirmed sample, hence this rule has not been applied

subject	nominal visit	visit date	c/mL	log10 c/mL	log10 decrease from BL	CV outcome	comments
	Baseline	02-Apr-15	303007				
	Week 4	30-Apr-15	270	2.43	3.05		
	Week 8	28-May-15	140	2.15	3.33		
	Week 16	23-Jul-15	29153	4.46	1.02	Suspected rebound	2 consecutive values <400, followed by an initial value >=400
	week 16 retest	26-Aug-15	454	2.66	2.82	Confirmed rebound	2 consecutive values <400, followed by 2 consecutive values >=400
	Withdrawal	17-Sep-15	<40	1.59	3.89		

11.6.6. Virology

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'

- **Treatment-emergent genotypic mutations** are defined as mutations that appear between baseline and an On-treatment assessment (e.g., at time of confirmed virologic withdrawal criteria).

Resistance Associated Mutations

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

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A/I/K**, L74M, **E92Q/V**/G, Q95K, T97A, G118R, F121Y, E138A/K/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, 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 (https://hivdb.stanford.edu/hivdb/by-mutations/http://hivdb.stanford.edu/DR/cgi-bin/rules_scores_hivdb.cgi?class=INI cited 28 Feb 2014) and accessed on 16 Feb 2015.
- 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 Wensing, 2014

Susceptibility Scores

Stanford Genotypic Susceptibility Score (GSS)

- To establish genotypic susceptibility to background treatment, a genotypic sensitivity score will be calculated.
- Genotypic sensitivity to each drug will be assessed using the HIVdb, the Integrated Genotypic Resistance Interpretation System [Liu, 2006].
- In the HIVdb system, each HIV-1 drug resistance mutation is assigned a drug penalty score. The penalty scores for each drug resistance mutation are available at
  NNRTI: https://hivdb.stanford.edu/dr-summary/mut-scores/NNRTI/
  NRTI: https://hivdb.stanford.edu/dr-summary/mut-scores/NRTI/
  PI: https://hivdb.stanford.edu/dr-summary/mut-scores/PI/
  INSTI: https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/. Scores for particular patterns of INSTIs are also available at https://hivdb.stanford.edu/dr-summary/pattern-scores/INSTI/
- The drug resistance estimate is obtained by adding together the penalty scores from all mutations associated with resistance to that drug and then a numeric score (S-GSS) is applied for each drug as shown below. The sum scores are titrated to fall within the following ranges: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance (see table below).

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

- For a drug which is not assessed by HIVdb (e.g., enfuvirtide), this drug will be assigned a numeric score of 0 if the fold change in resistance to that drug is above the cutoff defined by PhenoSense and 1 if below the cutoff (see Table 11). Maraviroc will be assigned a score of 0 if the virus is dual/mix tropic or X4 tropic or viral receptor tropism testing was not performed, and 1 if the virus is R5 tropic.
- 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)

- Genotypic sensitivity to each drug will be assessed using the Monogram resistance score for each background drug provided in the database.

Score	Sensitivity
1	Y
0	N

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

Phenotypic Susceptibility Score (PSS)

- 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 the phenotypic fold resistance to that drug at a certain timepoint (e.g., Screening or Baseline). A numeric score will be assigned to each background drug using two different methods: one with full sensitivity only (PSSf; Table 11) and one with partial sensitivity included (PSSp; Table 12).

Table 11 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

Table 12 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

- If only a biological cutoff is available, the algorithm for PSSf will be applied. Maraviroc will be assigned a score of 0 if the virus is dual/mix tropic or X4 tropic or viral receptor tropism testing was not performed, and 1 if the virus is R5 tropic.
- Both PSSf and PSSp will be calculated separately for each subjected 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]
Rilpivarine	RPV	NNRTI	2
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]

a. clinical cutoff (lower cutoff – higher cutoff)

Net Assessment for Optimised Susceptibility Scoring

Net assessment is an assessment of antiviral activity of background 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 not fully active in this analysis). For determining overall susceptibility of background ARTs (OSS), a binary scoring system (0= not fully active, 1= fully active) 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 background ART and categorised as 0, 1, 2, or >2.

Resistance Data from China

At the time of the Week 24 analysis not all of the phenotype data may be available from Monogram for subjects in China. The genotype data may be a mixture of Q2 and Monogram data, and in the event that both Q2 and Monogram are available at the same timepoint the Monogram data will be used.

Day 1 genotypic and phenotypic resistance data for RT and PRO is provided for all subjects by Monogram and will be used in the analysis. Subjects with CVW criteria will also have resistance testing performed by Monogram at SVW timepoints. PSS is only provided by Monogram. The

screening genotype from QUEST may be used if Monogram genotype is missing.

Definition of TAMS

TAMS are thymidine analogue mutations and are a combination of the thymidine analogues AZT (ZDV) mutations and d4T mutations in RT (reverse transcripitase). They can be found at the Stanford database, details are included in the following table:

	Thymidine Analog Mutations (TAMs)					
Amino acid position in RT	41	67	70	210	215	219
Wild type	M	D	K	T	T	K
Muations	L	N	R	W	FY	QE

11.6.7. Health Outcomes

HIVTSQs

[redacted]

[redacted]

MMAS-8

[redacted]

[redacted]

GSRS

[redacted]

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

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as: ○ Randomised to LPV/RTV + two NRTIs and completed the Randomised Phase including the Week 52 study visit; ○ Randomised to DTG + two NRTIs, completed the Randomised Phase including the Week 52 study visit, and did not enter the Continuation Phase; ○ Randomised to DTG + two NRTIs, completed the Randomised Phase, including the Week 52 study visit, entered and completed the Continuation Phase (defined as remaining on study until commercial supplies of DTG become locally available to patients [e.g. through public health services]). • Withdrawn subjects were not replaced in the study. • All available data from subjects who were withdrawn from the study will be listed.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Health Outcome	• See Section 11.6.7.

11.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before

Element	Reporting Detail
	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 Section 11.4. ○ Missing Stop Day: Last day of the month will be used ('28/29/30/31' dependent on the month and year), unless this is after the stop date of study treatment; in th0069s case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Prior/Concomitant Medications	• Partial dates for any prior/concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) 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. • Handling of completely missing start or end dates is discussed in Appendix 4: Treatment States and Phases.

11.7.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Snapshot (MSDF)	• 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'. Full details of the Snapshot algorithm are in Section 11.13. • For the Week 48 deliverable, there will be 3 versions of the Snapshot dataset relative to the Primary Estimand and Additional Estimands 1 & 2. For the Week 24 deliverable, there will only be one version of the dataset. •
LOCF	• In the LOCF dataset, missing values will be carried forward from the previous, non-missing available on-treatment assessment.
HO	• Missing data in the Health Outcome questionnaires are described in Section 11.6.7.
Lipids 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.

Element	Reporting Detail
	• Missing baseline 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 and analyses of lipids data

11.8. 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.

11.9. Appendix 9: Multicenter Studies

11.9.1. Methods for Handling Centres

Data will be summarised for all centres combined. Country will be treated as an exploratory subgroup for analyses of the primary efficacy endpoint as described in Section 7.1.2.

11.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

11.10.1. Handling of Covariates, Subgroups & 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 (See Section 7.1.2 and Section 9.1 for further details).
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Category	Covariates and / or Subgroups
Randomization Strata using Baseline Values	• Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL); • Number of fully active background NRTIs (<2 vs. 2) based on GSS at Baseline. For analysis purposes, randomization strata will be re-derived using Baseline values. In particular, fully active is defined at Baseline by the genotypic resistance reports of the central laboratory (or a laboratory contracted by the central laboratory) showing no evidence of full or of partial genotypic resistance for a given NRTI. If Baseline genotypic results are not available, then activity of the background regimen will be based on genotypic results at Screening. All statistical analyses will adjust for the above baseline randomization strata, unless stated otherwise. Treatment-by-Strata interactions will be assessed as specified in the analysis Section 7.1 (primary endpoint) and Section 8.1 (secondary endpoint analyses) and Section 9.1 (health outcomes analyses).
Background Regimen and Resistance Subgroups	• WHO recommended public-heath approach second-line NRTI background regimen (yes vs. No) (use definition in 11.6.3) • Baseline PSS to background regimen: (<2 vs. 2) • Baseline GSS to background regimen: (<2 vs. 2) • ABC+3TC vs not ABC+3TC

Demographic and Baseline Characteristic Subgroups	• Age: <35, 35-<50, ≥50
	• Race:
	  ○ White; Non-White
	  ○ African American/African Heritage; Non-African American/African Heritage

Category	Covariates and / or Subgroups

	• Sex:
	  ○ Female
	  ○ Male
	• Country
	• Baseline plasma HIV-1 RNA:
	  ○ <1000; 1000 to <10,000; 10,000 to <50,000; 50,000 to 100,000; >100,000 c/mL.
	  ○ ≤100,000, >100,000 c/mL
	• HIV-1 subtype:
	  ○ Subtype is found as part of the Monogram phenotype assay output. It is also known as clade eg, clade B = subtype B.
	• Baseline CD4+ cell count:
	  ○ ≤Y cells/mm3 or >Y cells/mm3 (Y=cutoff closest to median);
	  ○ <200, 200-<350, ≥350 cells/mm3
	• Baseline Centers for Disease Control and Prevention (CDC) category:
	  ○ CDC Category A,
	  ○ CDC Category B
	  ○ CDC Category C);

11.11. Appendix 11: Handling of Multiple Comparisons & Multiplicity

A pre-specified fixed sequence testing procedure is used to control for multiplicity: if the primary comparison is significant for NI at the 5% two-sided alpha level then testing for superiority will proceed at the 5% two-sided alpha level; otherwise testing of superiority will not be performed.

The interim analysis schedule does not require an adjustment for multiplicity since the IDMC analyses do not inflate the type I error rate to any measurable degree (see protocol Section 8.3.4.2), and the Week 24 interim analysis is supportive to the primary Week 48 analysis and will not be used to make definitive claims of a positive finding.

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

11.12.1. Statistical Analysis Assumptions

Endpoint(s)	• Change from Baseline in fasting LDL cholesterol at Weeks 24 and 48 • Change from Baseline in fasting TC/HDL ratio at Weeks 24 and 48 • HIV-Treatment Satisfaction Questionnaire (treatment satisfaction score) • Gastrointestinal Symptom Rating Scale (Individual scores)
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 used by specifying 'type=UN' 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.

11.13. Appendix 13: Snapshot

- Consider an arbitrary visit window, Week X (see Section 11.3).
- A subject's response (i.e., 'Virologic Success', 'Virologic Failure', or 'No Virologic Data at Week X') in that window is determined as indicated below, in the order stated.

1. If non-permitted change in background ART **prior** to Week X: Subject = Virologic Failure.
2. If permitted change in background ART **prior** to Week X AND decision to make this change is *after* the first On-treatment HIV-1 RNA result AND the latest On-treatment HIV-1 RNA result prior to the date of decision to switch is ≥ 50 c/mL: Subject = Virologic Failure.
3. If non-permitted change in background ART **during** Week X

   OR

   if permitted change in background ART **during** Week X AND decision to make this change is *after* the first On-treatment HIV-1 RNA result AND the latest On-treatment HIV-1 RNA result prior to the date of decision to switch is >=50 c/mL

   AND:

   - no HIV-1 RNA result is available during Week X prior to change: Subject = Virologic Failure;
   - there is at least one HIV-1 RNA result available during Week X prior to the change, then consider the latest such result:
     - If < 50 c/mL: Subject = Virologic Success
     - If ≥ 50 c/mL: Subject = Virologic Failure.
4. If there is no change in background ART **prior or during** Week X

   OR

   a permitted change **prior or during** Week X is decided on *before* the first On-treatment HIV-1 RNA result,

   OR

   a permitted change **prior or during** Week X is decided on *after* the first On-treatment RNA result AND the latest On-treatment HIV-1 RNA result prior to the decision to switch is <50 c/mL,

   AND

   at least one HIV-1 RNA result is available during Week X, then consider the latest such result:

   - If < 50 c/mL: Subject = Virologic Success;
   - If ≥ 50 c/mL: Subject = Virologic Failure.
5. If there is no change in background ART **prior or during** Week X

   OR

   a permitted change **prior or during** Week X is decided on *before* the first On-treatment HIV-1 RNA result

OR

a permitted change **prior or during** Week X is decided on *after* the first On-treatment RNA result AND the latest On-treatment HIV-1 RNA result prior to the decision to switch is <50 c/mL,

AND

no HIV-1 RNA results are available during Week X:

- If the subject has not withdrawn from the study prior to or during Week X: Subject = No Virologic Data at Week X, with a reason of 'Missing data during window but on study';
- If the subject was withdrawn from the study prior to or during Week X due to AE or death: Subject = No Virologic Data at Week X, with a reason of 'Discontinued due to AE or Death';
- Otherwise, consider the subject's last available On-treatment HIV-1 RNA result:
  - If <50 c/mL or no result is available: Subject = No Virologic Data at Week X, with a reason of 'Discontinued for Other Reasons';
  - If ≥ 50 c/mL: Subject = Virologic Failure.

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 time 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.*

<u>Optimized Background Therapy Substitutions After Randomisation</u>

- 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.

11.14. Appendix 14 – Q2 Creatinine Assay Accuracy Issue

11.14.1. Sensitivity Analyses

The machine at the central laboratory had debris in the system which led to suspect samples for creatinine. The impacted samples are indicated in the spreadsheet below.

Sensitivity analyses will be conducted excluding the suspect creatinine samples from any laboratory summaries. The details of the samples to be excluded are in the excel spreadsheet Suspect Creatinine Samples Study 200304 (Reference: RAP-Amend1-200304-Appendix 14.xls).

11.15. Appendix 15 – Abbreviations & Trade Marks

11.15.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
ABC	Abacavir
AdaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase
ART	Antiretroviral Treatment
ATC	Anatomical Therapeutic Chemical
ATV	Atazanavir
c/ml	Copies per milliliter
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CS	Clinical Statistics
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTR	Clinical Trial Register
CV	Cardiovascular
CVWC	Confirmed Virologic Withdrawal Criteria
DAIDS	Division of AIDS
DBF	Database Freeze
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ERDF	Efficacy Related Discontinuation = Failure
FC	Fold change
FDA	Food and Drug Agency
FDC	Fixed Dose Combination
FTC	Emtricitabine
FU	Follow-up
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
GSK	GlaxoSmithKline
GSRS	Gastrointestinal Symptom Rating Scale
GSS	Genotypic Susceptibility Score
GUI	Guidance

Abbreviation	Description
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HIV(-1)	Human immunodeficiency virus (type 1)
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HSR	Hypersensitivity reaction
IA	Interim Analysis
IAS-USA	International Antiviral Society-USA
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IN(I)	Integrase (Inhibitor)
IP	Investigational Product
ITT	Intent-To-Treat
ITT(e)	Intent-To-Treat Exposed
LDL	Low density lipoprotein
LOCF	Last Observation Carries Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMAS-8	Morisky 8-Item Medication Adherence Scale
MMRM	Mixed Model Repeated Measures
NCEP	National Cholesterol Education Program
NNRTI	Non-nucleoside Reverse Transcript Inhibitor
NRTI	Nucleoside Reverse Transcript Inhibitor
OC	Observed Case
OSS	Optimised Susceptibility Scoring
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PI	Protease Inhibitor
PP	Per Protocol
PSRAE	Possibly suicidality related Adverse Event
PSS	Phenotypic Susceptibility Score
QC	Quality Control
QTcB	Bazett's QT Interval Corrected for Heart Rate
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAMOS	Randomization & Medication Ordering System
RAP	Reporting & Analysis Plan
RNA	Ribonucleic acid
RTV	Ritonavir
RUCAM	Roussel Uclaf Causality Assessment Method
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model
SOC	System Organ Class

Abbreviation	Description
SOP	Standard Operation Procedure
SVW	Suspected Virologic Withdrawal
TA	Therapeutic Area
TC	Total Cholesterol
TDF/FTC	Tenofovir/emtricitabine
TFL	Tables, Figures & Listings
TRDF	Treatment Related Discontinuation = Failure
VF	Virologic Failure
WHO	World Health Organisation

11.15.2. Trademarks

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11.16. Appendix 16 – Example SAS code for Additional Estimand 2

```
*Presented below are excerpts of code that can be used for the multiple imputation steps
for the Additional Estimand 2 methodology for the Primary Efficacy Endpoint at Week 48;
*The code has not been extensively QC'ed therefore care must be taken when implementing;

*Programming Steps:
[1] Select LOG HIV-1 RNA data from ADLB
[2] Subset data by Treatment group
[3] Multiple Imputation on the Continuous scale
[3a]For LPV/RTV arm: run a simulation replacing BLQ with values from U(0,BLQ)
distribution;


* 100 simulated datasets;
data step3a ;
  set step3a ;
  do i=1 to 100;
    if substr(LBSTRESC,1,1)="<" then aval2 = rand('uniform')*1.59;
                    *i.e. 1.59 is slightly below log(50) hence BLQ;
    else aval2=aval;
        _imputation_ = i;
        output;
  end;
  drop i;
run;

*Programming steps continued:
[3b] Transpose datasets LPV/RTV & DTG datasets ready for MI
[3c] For LPV/RTV subjects, PROC MI to create Monotone structure;


*** Note: AVAL1 = Week 1 (baseline), to AVAL52 (Week 52);
*** Programming Note: add stratification factors;
proc mi data=step3c out=DATAIN_MONO nimpute=1 seed=200304;
    by _imputation_;
        var AVAL1 AVAL4 AVAL8 AVAL16 AVAL24 AVAL36 AVAL48 AVAL52;
        mcmc impute=monotone;
run;

*Programming steps continued:
[3d] Impute the remaining monotone missing values

*** Assumption: MAR;
data DATAIN_MONO (rename=(_Imputation_=Imputation));
  set DATAIN_MONO ;
run;

*** Programming Note: add stratification factors;
proc mi data= DATAIN_MONO out= DATAIN_REG nimpute=1 seed=200304;
        by Imputation;
        var AVAL1 AVAL4 AVAL8 AVAL16 AVAL24 AVAL36 AVAL48 AVAL52;
        monotone regression;
run;


data DATAIN_REG;
  set DATAIN_REG;
  rename Imputation = _impute_;
run;

*Programming steps continued:
[4] Merge DTG to LPV/RTV imputed dataset. For DTG dataset, create duplicate rows (=number
of imputed datasets)

data step4dtg ;
  set step4dtg;
  _impute_=1;
  do _impute_= 1 to 100;
```

```
  output;
  end;
run;

*Programming steps continued:
[5a] Remove non-IDMC affected subjects from LPV/RTV imputed dataset.
[5b] Merge original data of non-IDMC LPV/RTV subjects LPV/RTV imputed, replacing imputed
data for these subjects with original observations. Do so by creating duplicate rows
(=number of imputed datasets)
[6] apply Snapshot algorithm
[7a] Perform CMH test & obtain Mantel-Haenszel estimate of the common odds ratio & P-
value;

*programming note: need to add stratification factors;
*take care when specifying tables statement;

proc freq data=step7;
  tables trt01p * snapresp /cmh riskdiff measures ;
  by _impute_ ;
  ODS OUTPUT CMH=cmh COMMONRELRISKS=comrrout CrossTabFreqs  = Freqout
measures=measures_est riskdiffcol1=riskdiff_est;
RUN;


data Prop (keep= p SEp TREAT _impute_ );
  set riskdiff_est ;
  p=1-risk;
  SEp=ase;
  if Row in("Row 1","Row 2");
       if Row="Row 1" then TREAT="DTG    ";
  else if Row="Row 2" then TREAT="LPV/RTV";
run;

proc sort data=PROP;
  by TREAT ;
run;

*Programming steps continued:
[7b] Combine results;
PROC MIANALYZE DATA=prop ;
  modeleffects p ;
  stderr SEp;
  by TREAT ;
RUN;

*Programming steps continued:
[7c] for the P-value, apply Wilson-Hilferty transformation to the CMH statistic and
standardize the resulting normal variable;

DATA cmh_wh;
  SET cmh(WHERE=(AltHypothesis="General Association"));
  cmh_value_wh=((VALUE/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
  cmh_sterr_wh = 1.0;
RUN;

*Programming steps continued:
[7d] Combine results;
PROC MIANALYZE DATA=cmh_wh;
  ODS OUTPUT PARAMETERESTIMATES=mian_cmh_wh;
  MODELEFFECTS cmh_value_wh;
  STDERR cmh_sterr_wh;
RUN;

*Programming steps continued:
[7e] Compute one-sided p-value;
DATA mian_cmh_wh_p;
  SET mian_cmh_wh;
  IF tValue > 0 THEN Probt_upper = Probt/2;
  ELSE Probt_upper = 1-Probt/2;
RUN;
```

11.17. Appendix 17: List of Data Displays

11.17.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Pharmacodynamic and / or Biomarker	5.1 to 5.n	5.1 to 5.n
Pharmacokinetic / Pharmacodynamic	6.1 to 6.n	6.1 to 6.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

11.17.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in a separate document.

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
Virology	VI_Fn	VI _Tn	VI _Ln
Health Outcome	HO_Fn	HO_Tn	HO_Ln

NOTES:

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

11.17.3. Deliverable

Delivery	Description
24 Week	Interim Analysis Statistical Analysis Complete
48 Week	Primary Statistical Analysis Complete

The following phases are defined: R=Randomised Phase and RC=Randomised Phase and ContinuationPhase.

Phase of the deliverable labelled as R/RC means that the output will initially be created based on the Randomised Phase only then repeated based on the Randomised Phase and Continuation Phase. Deliverables without a Phase are assumed to be for the Randomised phase only

11.17.4. Study Population

11.17.4.1. Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Subject disposition					
1.1.	All Subjects Screened	SP1	Summary of Study Populations	CS CORE	24wk, 48wk
1.2.	All Subjects Screened	NS1	Summary of Subjects by Country and Investigator	CS CORE	24wk, 48wk
1.3.	ITT-E	EudraCT age DM11	Summary of Age Categories	CS CORE	24wk, 48wk
1.4.	All Subjects Screened	ES6	Summary of Reasons for Screen Failure	CS CORE	24wk, 48wk
1.5.	ITT-E	ES1	Summary of Subject Accountability: Study Conclusion Record		24wk, 48wk
1.6.	ITT-E	ES1	Summary of Subject Accountability: Randomised Phase Conclusion Record		24wk, 48wk
1.7.	ITT-E	ES1	Summary of Subject Accountability: Continuation Phase Conclusion Record		24wk, 48wk
1.8.	ITT-E	HIV_ES1	Summary of Subject Accountability: Withdrawals by Visit		24wk, 48wk
1.9.	ITT-E	SD1	Summary of Treatment Status		
1.10.	ITT-E	DV1	Summary of Important Protocol Deviations	CS CORE	24wk, 48wk
1.11.	ITT-E	SP2	Summary of Protocol Deviations Leading to Exclusion from the Per-Protocol Population	CS CORE. Only deviations occurring in the period of interest can lead to exclusion from the PP Population.	24wk, 48wk
1.12.	ITT-E	IE1	Summary of Inclusion/Exclusion Criteria Deviations		24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Demography					
1.13.	ITT-E	DM1	Summary of Demographic Characteristics	CS CORE	24wk, 48wk
1.14.	ITT-E	DM5	Summary of Race and Racial Combinations	CS CORE	24wk, 48wk
1.15.	ITT-E	DM6	Summary of Race and Racial Combinations Details	CS CORE	24wk, 48wk
1.16.	ITT-E	DM8	Summary of All Indicated Races		
1.17.	ITT-E	CDC1	Summary of CDC Classification of HIV Infection at Baseline		24wk, 48wk
1.18.	ITT-E	Shell POP_T1 gsk2619619/ing 117172/week48 /drivers/cr_t_cvr f.sas	Summary of Baseline Cardiovascular Risk Assessments		24wk, 48wk
1.19.	ITT-E	Shell POP_T2 gsk2619619/ing 117172/week48 /drivers/vl_t_scr nbl_hivrna.sas	Distribution of Quantitative Plasma HIV-1 RNA Results at Screening and Baseline	Include a category of viral load <400 especially for screening (ie to identify screening failure). Added <400 at baseline too.	24wk, 48wk
1.20.	ITT-E	Shell POP_T3 gsk2619619/ing 117172/week48 /drivers/vl_t_scr nbl_cd4.sas	Distribution of CD4+ Cell Count (cells/mm^3) Results at Screening and Baseline		24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
1.21.	ITT-E	Shell POP_T4 gsk2619619/ing 117172/week48 /drivers/lb_t_he p.sas	Summary of Hepatitis Status at Entry		24wk, 48wk
Medical Condition & Concomitant Medications					
1.22.	ITT-E	MH1	Summary of Current Medical Conditions	CS CORE	24wk, 48wk
1.23.	ITT-E	MH1	Summary of Past Medical Conditions	CS CORE	24wk, 48wk
1.24.	ITT-E	MH4	Summary of Current Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		24wk, 48wk
1.25.	ITT-E	MH4	Summary of Past Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		24wk, 48wk
1.26.	ITT-E	CM1	Summary of Concomitant Medication by Ingredient ATC Level 1	CS CORE	24wk, 48wk
1.27.	ITT-E	CM8	Summary of Concomitant Medication Ingredient Combinations		24wk, 48wk
1.28.	ITT-E	CM1b	Summary of Concomitant Medication by Combination Term ATC Level 1		24wk, 48wk
1.29.	ITT-E	Shell POP_T5 gsk1349572/ing 111762/week48 /drivers/cm_t_p rior.sas	Summary of Prior Antiretroviral Therapy at the time of Screening		24wk, 48wk
1.30.	ITT-E	Use shell for POP_T5	Summary of Prior Antiretroviral Therapy discontinued prior to Screening		24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
1.31.	ITT-E	Shell POP_T6	Summary of Prior Antiretroviral Therapy at the time of screening – First line combination	New output	24wk, 48wk
1.32.	ITT-E	Shell POP_T7 /arenv/arprod/gsk1349572/ing111762/week48/drivers/cm_t_prinum.sas	Summary of Prior Antiretroviral Therapy Classes at time of Screening	Only create if we have more than 10 subjects with a prior ART other than NNRTI+NRTI.	24wk, 48wk
1.33.	ITT-E	Shell POP_T8 gsk1349572/ing111762/week48/drivers/cm_t_pridur.sas	Summary of Duration of Prior Antiretroviral Therapy at time of Screening		24wk, 48wk
1.34.	ITT-E	Shell POP_T9 gsk1349572/ing111762/week48/drivers/cm_t_day1.sas	Summary of Background Antiretroviral Therapy Received at Time of IP Start by Agent Combination		24wk, 48wk
1.35.	ITT-E	Shell POP_T10 gsk1349572/ing111762/week48/drivers/cm_t_lipid_bl.sas	Summary of Lipid Modifying Agent Use at Baseline		24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
1.36.	ITT-E	Shell POP_T11 gsk1349572/ing111762/week48/drivers/cm_t_lipid_postbl.sas	Summary of Lipid Modifying Agent Use Starting Post-Baseline		24wk, 48wk
Virology					
1.37.	ITT-E	Shell POP_T12 ing111762/week48/drivers/cm_t_classres.sas	Summary of the Number of Baseline Major Mutations Associated with the Resistance to NRTI, NNRTI, and PI drug classes		24wk, 48wk
1.38.	ITT-E	Shell POP_T13 gsk1349572/ing111762/week48/drivers/mu_t_bl_maj_oth.sas	Summary of the Number of Baseline Major Substitution to NRTI, NNRTI and PI Drug Classes		
1.39.	All Screened Subjects	Shell POP_T14	Proportion of subjects without at least 1 fully active NRTI		24wk, 48wk
1.40.	All Screened Subjects	Shell POP_T15 ing111762/week48/drivers/cm_t_classres.sas	Summary of the Number of Screening Major Mutations Associated with the Resistance to NRTI, NNRTI, and PI drug classes	Screening genotypic data is all from Q2. There may be some subtle differences to discuss with programmers compared with the Monogram data. For Q2 if there is an insertion it may not be possible to determine precise order.	24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
1.41.	All Screened Subjects	Shell POP_T16 gsk1349572/ing 111762/week48 /drivers/mu_t_bl _maj_oth.sas	Summary of the Number of Screening Major Substitution to NRTI, NNRTI and PI Drug Classes	Screening genotypic data is all from Q2. There may be some subtle differences to discuss with programmers compared with the Monogram data. For Q2 if there is an insertion it may not be possible to determine precise order.	24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**

1.42.	ITT-E	Shell POP_T17	Summary of Baseline Major NNRTI and NRTI Mutations	New table which includes:
				• Number of thymidine analogue-associated mutations (TAMS): 1, 2, >2
				• Prevalence of
				  ○ L65A or L70G
				  ○ 69 insertion complex
				  ○ 151 insertion complex
				  ○ Other major NRTI mutations
				• Prevalence of
				  ○ M184V only
				  ○ M184V with any other major NRTI mutation
				[proposed new output to match that of the SECONDLINE Kirby manuscript]
					24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
1.43.	ITT-E	Shell POP_T18 gsk1349572/ing111762/week24/drivers/ph_t_bl_geno_gssd11.sas	Summary of Stanford Baseline GSS to Background ART Regimen		24wk, 48wk
1.44.	ITT-E	Shell POP_T19 gsk1349572/ing111762/week24/drivers/ph_t_bl_geno_gssd11.sas	Summary of Monogram Baseline GSS to Background ART Regimen	New table. Use summary of Stanford GSS summary as a shell.	24wk, 48wk
1.45.	ITT-E	Shell POP_T20 gsk1349572/ing112574/week48/drivers/ph_t_bossfbng_d8.sas	Summary of Baseline OSS (Net Assessment) to Background Therapy	Viking T12.71	24wk, 48wk
1.46.	ITT-E	Shell POP_T21 sk1349572/ing111762/week24/drivers/ph_t_basepss.sas	Summary of Baseline PSS to Background ART Regimen		24wk, 48wk

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
1.47.	ITT-E	Shell POP_T22 gsk1349572/ing111762/week24/drivers/mu_t_hiv_clades.sas	Summary of the Prevalence of HIV-1 Clades at Baseline by Frequency	Use Monogram Testing For W24, for **China** we will have mostly Q2 genotype and just a few Monogram testings of the samples that we were able to export for testing.	24wk, 48wk
1.48.	ITT-E	Shell POP_T23	Summary of First Line Regimen and Expected Second Line Regimen Using the WHO Algorithm	New table	24 wk, 48 wk
1.49.	ITT-E	Shell POP_T24	Summary of Expected WHO Second Line vs. Background Regimen actually Taken	New table	24 wk, 48 wk

11.17.5. Efficacy

11.17.5.1. Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Primary					
2.1.	ITT-E	Shell EFF_T1 gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 – Snapshot Analysis		24wk, 48wk
2.2.	Per-Protocol	Shell EFF_T2	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 – Snapshot Analysis		24wk48wk
2.3.	Intent to treat	Shell EFF_T3	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 – Snapshot Analysis		24wk, 48wk
2.4.	ITT-E	Shell EFF_T4 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 24/48 – Snapshot Analysis		24wk, 48wk
2.5.	ITT-E	Shell EFF_T6 gsk2619619/ing117172/week48/drivers/t_snap_sum_prop_p.sas	Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48-Snapshot Analysis		24wk, 48wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.6.	ITT-E	Shell EFF_T7 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 24/48 – by number of fully active background NRTIs		24wk, 48wk
2.7.	ITT-E	Shell EFF_T8 gsk2619619/ing117172/week48/drivers/t_snap_sum_prop.sas	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48by Subgroup - Snapshot Analysis	Note: only present by ABC+3TC vs non ABC+3TC if more than 10 subjects took ABC+3TC	24wk, 48wk
2.8.	ITT-E	Shell EFF_T9 gsk2619619/ing117172/week48/drivers/t_snap_prop_50.sas	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit - Snapshot Analysis		24wk, 48wk
2.9.	ITT-E	Shell EFF_T10 gsk2619619/ing117172/week48/drivers/t_snap_prop_50.sas	Proportion of Subjects with Plasma HIV-1 RNA<50 c/mL by Visit and Subgroup –Snapshot Analysis	Adapt program to include subgroups	24wk, 48wk
2.10.	ITT-E	Shell EFF_T11 gsk2619619/ing117172/week48/drivers/t_snap_prop_400.sas	Proportion of Subjects with Plasma HIV-1 RNA <400 c/mL by Visit - Snapshot Analysis		24wk, 48wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.11.	ITT-E	Shell EFF_T12 gsk2619619/ing117172/week48/drivers/t_sn_studout_400.sas	Summary of Study Outcomes (<400 c/mL) at Week X – Snapshot Analysis		24wk, 48wk
2.12.	ITT-E	Shell EFF_T13 gsk2619619/ing117172/week48/drivers/t_ef_km_trdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal Criteria at Week 48 - *Treatment Related Discontinuation* = *Failure*	TTE6	24wk, 48wk
2.13.	ITT-E	Shell EFF_T14 gsk2619619/ing117172/week48/drivers/t_ef_km_erdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal Criteria at Week 48 - *Efficacy Related Discontinuation* = *Failure*	TTE6	24wk, 48wk
2.14.	ITT-E	Shell EFF_T15 /arenv/arprod/gsk1349572/ing114467/week48/drivers/ef_t_pdvf_vis.sas	Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit		24wk, 48wk
2.15.	ITT-E	Shell EFF_T16 /arenv/arprod/gsk1349572/ing111762/week48/drivers/ef_t_pdvf_vis.sas	Cumulative Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit by Type of Virologic Failure		24wk, 48wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.16.	ITT-E	Shell EFF_T17 gsk1349572/ing111762/week48/drivers/ef_t_pdvf_dist.sas	Distribution of Quantitative Plasma HIV-1 RNA Results at Suspected and Confirmation of Virologic Withdrawal Criteria		24wk, 48wk
2.17.	ITT-E	Shell EFF_T18 gsk1349572/ing114915/week48/drivers/ef_t_km_timeto_sup50.sas	Summary of Kaplan-Meier Estimates of Time to Viral Suppression (HIV-1 RNA <50 c/mL)		24wk, 48wk
2.18.	ITT-E	Shell EFF_T19	Proportion of Subjects With Detectable Viral Load Below the Limit of Quantification at Week 24/48		24wk, 48wk
2.19.	ITT-E	HIV1	Summary of Post-Baseline HIV-1 Associated Conditions Including Recurrences		24wk, 48wk
2.20.	ITT-E	HIV1	Summary of Post-Baseline HIV-1 Associated Conditions Excluding Recurrences		24wk, 48wk
2.21.	ITT-E	HIV2	Summary of Post-Baseline HIV-1 Disease Progressions		24wk, 48wk
2.22.	ITT-E	Shell EFF_T19 gsk2619619/ing117172/week48/drivers/ef_t_cd4_chg.sas	Summary of Change from Baseline in CD4+ Cell Count (cells/mm^3) by Visit		24wk, 48wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.23.	ITT-E	Shell EFF_T20 gsk2619619/ing117172/week48/drivers/t_ef_hv1rn_chg.sas	Summary of Change from Baseline in Plasma HIV-1 RNA (log10 c/mL) by Visit		24wk, 48wk
2.24.	ITT-E	Shell EFF_T21 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week X by [Subgroup] – Snapshot Analysis	As Needed. Modify program to present by subgroups.	24wk, 48wk
2.25.	ITT-E	Shell EFF_T1 gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis – Additional Estimand 1		48wk
2.26.	ITT-E	Shell EFF_T4 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 48 – Snapshot Analysis – Additional Estimand 1		48wk
2.27.	ITT-E	Shell EFF_T1 gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis – Additional Estimand 2		48wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.28.	ITT-E	Shell EFF_T4 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 48 – Snapshot Analysis – Additional Estimand 2		48wk
2.29.	MITT-E-36	Shell EFF_T1 gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 36 – Snapshot Analysis		24wk
2.30.	MITT-E-36	Shell EFF_T4 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 36 – Snapshot Analysis		24wk
2.31.	MITT-E-48	Shell EFF_T1 gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis		24wk
2.32.	MITT-E-48	Shell EFF_T4 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 48 – Snapshot Analysis		24wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.33.	MITT-E-36	Shell EFF_T13 gsk2619619/ing117172/week48/drivers/t_ef_km_trdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal Criteria at Week 36 - *Treatment Related Discontinuation = Failure*	TTE6	24wk
2.34.	MITT-E-48	Shell EFF_T13 gsk2619619/ing117172/week48/drivers/t_ef_km_trdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal Criteria at Week 48 - *Treatment Related Discontinuation = Failure*	TTE6	24wk
2.35.	ITT-E	Shell EFF_T13 gsk2619619/ing117172/week48/drivers/t_ef_km_trdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal Criteria at Week 48 - *Treatment Related Discontinuation = Failure – Sensitvity Analysis*	TTE6	48wk
2.36.	ITT-E	Shell EFF_T14 gsk2619619/ing117172/week48/drivers/t_ef_km_erdf.sas	Summary of Kaplan-Meier Estimates of Proportion of Subjects Without Confirmed Virologic Withdrawal Criteria at Week 48 - *Efficacy Related Discontinuation = Failure – Sensitvity Analysis*	TTE6	48wk
2.37.	ITT-E	Shell EFF_T1 gsk2619619/ing117172/week48/drivers/t_ef_analprop.sas	Summary of Analysis of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis – Projected Estimate		24wk

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.38.	ITT-E	Shell EFF_T4 gsk2619619/ing117172/week48/drivers/t_sn_studout.sas	Summary of Study Outcomes (<50 c/mL) at Week 48 – Snapshot Analysis – Projected Estimate		24wk

11.17.5.2. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.1.	ITT-E	Shell EFF_F1 gsk2619619/ing117172/week48/drivers/ef_f_p50.sas	Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL by Visit – Snapshot Analysis	Week 24: Up to Week 24 Data Week 48: Up to Week 48 Data	24wk, 48wk
2.2.	ITT-E	Shell EFF_F2 gsk2619619/ing117172/week48/drivers/ef_f_diffprop.sas	Unadjusted Treatment Difference in Proportion (95%) of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 by Subgroup – Snapshot Analysis		24wk, 48wk
2.3.	ITT-E	Shell EFF_F3 gsk2619619/ing117172/week48/drivers/ef_f_p50.sas	Proportion (95% CI) of Subjects with HIV-1 RNA <400 c/mL by Visit – Snapshot Analysis	Use <400 cut-off instead of <50 cut-off Week 24: Up to Week 24 Data Week 48: Up to Week 48 Data	24wk, 48wk
2.4.	ITT-E	Shell EFF_F4 gsk1349572/ing111762/week48/drivers/ef_f_km_trdf.sas	Kaplan-Meier Plot of Time to Failure by Week 24– Treatment Related Discontinuation = Failure		24wk, 48wk

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
2.5.	MITT-E-36	Shell EFF_F4 gsk1349572/ing111762/week48/drivers/ef_f_km_trdf.sas	Kaplan-Meier Plot of Time to Failure by Week 36– Treatment Related Discontinuation = Failure		24wk
2.6.	MITT-E-48	Shell EFF_F4 gsk1349572/ing111762/week48/drivers/ef_f_km_trdf.sas	Kaplan-Meier Plot of Time to Failure by Week 48 – Treatment Related Discontinuation = Failure		24wk
2.7.	ITT-E	Shell EFF_F5 gsk1349572/ing111762/week48/drivers/ef_f_km_erdf.sas	Kaplan-Meier Plot of Time to Failure –Efficacy Related Discontinuation = Failure		24wk, 48wk
2.8.	ITT-E	Shell EFF_F6	Individual Plasma HIV-1 RNA (log10 c/mL) Profiles by Visit		24wk, 48wk
2.9.	ITT-E	Shell EFF_F7	Change from Baseline in CD4+ Cell Count (cells/mm^3) by visit	New figure	24wk, 48wk

11.17.6. Safety

11.17.6.1. Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Adverse Events					
3.1.	Safety	Shell SAFE_T1 gsk2619619/ing 117172/week48/ drivers/ex_t_exp osure_rand.sas	Summary of Extent of Exposure to Investigational Product for the Randomised Phase	CS Core	24wk, 48wk
3.2.	Safety	Shell SAFE_T2 gsk2619619/ing 117172/week48/ drivers/ex_t_exp osure.sas	Summary of Extent of Exposure to Investigational Product for the Randomised and Continuation Phases		24wk, 48wk
3.3.	Safety	Shell SAFE_T3 gsk1349572/ing 114467/week48/ drivers/ae_t_stat s_neuro_psych. sas	Statistical Analysis of Grade 2 or greater Drug-Related Diarrhoea	New output.	24wk, 48wk
3.4.	Safety	AE1	Summary of All Adverse Events by System Organ Class	CS Core (optional)	24wk, 48wk R, RC
3.5.	Safety	AE5B	Summary of All Adverse Events by System Organ Class and Maximum Toxicity	CS Core	24wk, 48wk R, RC
3.6.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency	CS Core	24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.7.	Safety	AE3	Summary of Common (>=5%) Grade 2-4 Adverse Events by Overall Frequency	CS Core	24wk, 48wk
3.8.	Safety	AE1	Summary of All Grade 2-4 Adverse Events by System Organ Class		24wk, 48wk
3.9.	Safety	AE5B	Summary of All Drug-Related Adverse Events by System Organ Class and Maximum Toxicity	CS Core	24wk, 48wk R, RC
3.10.	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class	CS Core	24wk, 48wk
3.11.	Safety	AE3	Summary of Common (>=5%) Drug-Related Grade 2-4 Adverse Events by Overall Frequency	CS Core	24wk, 48wk
3.12.	Safety	AE1	Summary of All Drug-Related Grade 2-4 Adverse Events by System Organ Class		24wk, 48wk
3.13.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class	CS Core	24wk, 48wk R, RC
3.14.	Safety	AE3	Summary of Drug-Related Fatal Serious Adverse Events		24wk, 48 wk
3.15.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class	CS Core	24wk, 48wk
3.16.	Safety	AE3	Summary of Non-Fatal Serious AEs		24wk, 48wk
3.17.	Safety	AE3	Summary of Drug-Related Non-Fatal Serious Adverse Events		24wk, 48wk
3.18.	Safety	AE1	Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product	CS Core	24wk, 48wk R, RC
3.19.	Safety	AE1	Summary of Common (>5%) Non-Serious Adverse Events	CS Core FDAAA 'Common' to be defined by study/project team, in accordance with FDAAA requirements. Use >5% cut-off	24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.20.	Safety	EudraCT Non-serious AE AE15	Summary of Subjects and Number of Occurrences of Common Non-Serious Adverse Events by System Organ Class	CS Core EudraCT For studies with very few events/subjects listing is sufficient.	24wk, 48wk
3.21.	Safety	EudraCT SAE AE16	Summary of Subjects and Number of Occurrences of Serious, Drug-Related Serious, Fatal, and Drug-Related Serious Adverse Events	CS Core EudraCT For studies with very few SAEs/subjects listing is sufficient.	24wk, 48wk
3.22.	Safety	AE3	Summary of Fatal Serious Adverse Events	CS Core GSK CTR For studies with very few fatal SAEs, listing is sufficient	24wk, 48wk
3.23.	Safety	AE3	Summary of Most Frequent Adverse Events by Overall Frequency		24wk, 48wk
3.24.	Safety	Shell SAFE_T4 gsk3365791/mid_dori_ph3/week48/drivers/t_ae_cum_er_srd1.sas	Summary of Cumulative Adverse Events by Visit	See DORI	24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Laboratory Values					
3.25.	Safety	Shell SAFE_T5 Use the non standard program in the ARIA study gsk2619619/ing 117172/week48/ drivers/t_stat_tri g_mar.sas	Statistical analysis of Change from Baseline in fasting LDL cholesterol at Weeks 24/48 (Multiple imputations – MAR)		24wk, 48wk
3.26.	Safety	Shell SAFE_T6 From ARIA: gsk2619619/ing 117172/week48/ drivers/t_stat_tri g_oc.sas	Statistical analysis of Change from Baseline in fasting LDL cholesterol at Weeks 24/48 by Visit – ANCOVA – Observed Case		24wk, 48wk
3.27.	Safety	Shell SAFE_T7 From ARIA gsk2619619/ing 117172/week48/ drivers/t_stat_tri g_locf.sas	Statistical analysis of Change from Baseline in fasting LDL cholesterol at Weeks 24/48 by Visit – ANCOVA – LOCF		24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.28.	Safety	Shell SAFE_T8 Use the non standard program in the ARIA study gsk2619619/ing 117172/week48/ drivers/t_stat_trig_mar.sas	Statistical analysis Change from Baseline in fasting TC/HDL ratio at Weeks 24/48 (Multiple imputations – MAR)	Use Shell SAFE_T5	24wk, 48wk
3.29.	Safety	Shell SAFE_T9 From ARIA gsk2619619/ing 117172/week48/ drivers/t_stat_trig_oc.sas	Statistical analysis Change from Baseline in fasting TC/HDL ratio at Weeks 24/48 by Visit - ANCOVA – Observed Case	Use Shell SAFE_T6	24wk, 48wk
3.30.	Safety	Shell SAFE_T10 From ARIA gsk2619619/ing 117172/week48/ drivers/t_stat_trig_locf.sas	Statistical analysis Change from Baseline in fasting TC/HDL ratio at Weeks 24/48 by Visit - ANCOVA – Lipids LOCF	Use Shell SAFE_T7	24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.31.	Safety	Shell SAFE_T11 (Famingo SAS code may be useful - gsk1349572/ing 114915/week48/ drivers/lb_t_stat s_incid_grad2_l dl.sas)	Statistical analysis of Maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24/48	New output	24wk, 48wk
3.32.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit	CS Core	24wk, 48wk
3.33.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit – Sensitivity Analysis Excluding Suspect Creatinine Samples	CS Core	24wk, 48wk
3.34.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit – Lipids and Glucose in Conventional Units		24wk, 48wk
3.35.	Safety	LB1	Summary of Hematology Changes From Baseline by Visit	CS Core	24wk, 48wk
3.36.	Safety	Shell SAFE_T12 gsk2619619/ing 117172/week48/ drivers/lb_t_max _tox_rand.sas	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities	CS Core	24wk, 48wk R, RC
3.37.	Safety	Repeat SAFE_T12	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities - Sensitivity Analysis Excluding Suspect Creatinine Samples	CS Core	24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.38.	Safety	Shell SAFE_T13 gsk2619619/ing 117172/week48/ drivers/lb_t_max _tox_haem_ran d.sas	Summary of Maximum Post-Baseline Emergent Hematology Toxicities	CS Core	24wk, 48wk R, RC
3.39.	Safety	Shell SAFE_T14 gsk2619619/ing 117172/week48/ drivers/lb_t_nce p_tri.sas	Summary of Changes in NCEP Lipid Baseline Category to Maximum Post-Baseline Category - Triglycerides		24wk, 48wk
3.40.	Safety	Shell SAFE_T15 gsk2619619/ing 117172/week48/ drivers/lb_t_nce p_tot.sas	Summary of Changes in NCEP Lipid Baseline Category to Maximum Post-Baseline Category – Total Cholesterol		24wk, 48wk
3.41.	Safety	Shell SAFE_T16 gsk2619619/ing 117172/week48/ drivers/lb_t_nce p_hdl.sas	Summary of Changes in NCEP Lipid Baseline Category to Maximum Post-Baseline Category – HDL Cholesterol		24wk, 48wk

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.42.	Safety	Shell SAFE_T17 gsk2619619/ing117172/week48/drivers/lb_t_ncep_ldl.sas	Summary of Changes in NCEP Lipid Baseline Category to Maximum Post-Baseline Category – LDL Cholesterol		24wk, 48wk
3.43.	Safety	VS1	Summary of Vital Signs		24wk, 48wk
3.44.	Safety	VS1	Summary of Change From Baseline in Vital Signs by Visit	CS Core Will only be produced if post-baseline data collected	24wk, 48wk
3.45.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		24wk, 48wk
3.46.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities Including the Continuation phase		24wk, 48wk RC
3.47.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	If a liver stopping event is reported	24wk, 48wk
3.48.	Safety	Shell SAFE_T18 gsk3365791/mid_dori_ph3/week48/drivers/t_cssrsib.sas	Summary of C-SSRS Suicidal Ideation or Behaviour during Treatment Excluding Incomplete Calls	Use DORI	24wk, 48wk

11.17.6.2. Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.1.	Safety	AE10	Plot of Common Adverse Events and Relative Risk	CS CORE	24wk, 48wk
3.2.	Safety	Shell SAFE_F1 /arenv/arprod/gsk1349572/ing114467/wk144/drivers/ef_f_cd4cfb_bywk.sas	Line Plot of Adjusted Mean (95% CI) Change From Baseline in Fasting LDL Cholesterol (units) Over Time - Repeated Measure Mixed Model		24wk, 48wk
3.3.	Safety	Shell SAFE_F2 /arenv/arprod/gsk1349572/ing114467/wk144/drivers/ef_f_cd4cfb_bywk.sas	Line Plot of Adjusted Mean (95% CI) Change From Baseline in Fasting TC/HDL ratio (units) Over Time - Repeated Measure Mixed Model		24wk, 48wk
3.4.	Safety	LIVER9	Scatter Plot of Maximum vs. Baseline for ALT	CS CORE. Add line of equality.	24wk, 48wk
3.5.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	CS CORE. Lloyd would like to see theALT on the horizontal axis and Bilirubin on the vertical axis, is it possible to update the standard?	24wk, 48wk

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.6.	Safety	Shell SAFE_F3 /arenv/arprod/gsk2619619/ing117172/wk48/drivers/sff_f_bar_trig.sas	Bar Chart of Triglycerides (mmol/L) NCEP categories at Week 24/48 vs Baseline	Copy from ARIA	24wk, 48wk
3.7.	Safety	Shell SAFE_F4 /arenv/arprod/gsk2619619/ing117172/wk48/drivers/sff_f_bar_chol.sas	Bar Chart of Total Cholesterol (mmol/L) NCEP categories at Week 24/48 vs Basline		
3.8.	Safety	Shell SAFE_F5 /arenv/arprod/gsk2619619/ing117172/wk48/drivers/sff_f_bar_hdl.sas	Bar Chart of HDL Cholesterol (mmol/L) NCEP categories at Week 24/48 vs Baseline		

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
3.9.	Safety	Shell SAFE_F6 /arenv/arprod/gsk2619619/ing117172/wk48/drivers/sff_f_bar_ldl.sas	Bar Chart of LDL Cholesterol (mmol/L) NCEP categories at Week 24/48 vs Baseline		
3.10.	Safety	Shell SAFE_F7 /arenv/arprod/gsk1349572/ing_psap/trii_iss_mar/drivers/lb_f_lft_prof.sas	Liver Chemistry Profile Plots for Subjects with Elevations at Any Post-Baseline Visit		24wk, 48wk

11.17.7. Virology

11.17.7.1. Tables

Virology: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Genotype					
4.1.	ITT- E	Shell VI_T1 gsk1349572/ing111762/week48/drivers/mu_t_gen_acc_48.sas	Summary of Subject Accountability: Genotypes Available	We might want to note the China data in this dataset since is different assay	24wk, 48wk
4.2.	CVW Genotypic	Shell VI_T2 /arenv/arprod/gsk1349572/ing114467/week48/drivers/mu_t_othmut_emrg.sas	Summary of Treatment Emergent Major Mutations of NRTI, NNRTI and PI Classes		24wk, 48wk
4.3.	CVW Genotypic	Shell VI_T3 /arenv/arprod/gsk1349572/ing111762/week48/drivers/mu_t_ini_te_pss48.sas	Summary of Pre-specified Treatment Emergent IN Substitutions at Time of Confirmed Virologic Withdrawal	Replace columns: Baseline PSSf to Background Regimen with treatment arms	24wk, 48wk

Virology: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
4.4.	CVW Genotypic	Shell VI_T4 /arenv/arprod/gsk1349572/ing111762/week48/drivers/ph_t_bl_geno_gsspdvf_48.sas	Summary of Changes in Genotypic Susceptibility (GSS) to Background ART Therapy at Time of Confirmed Virologic Withdrawal		24wk, 48wk
Phenotype					
4.5.	CVW Phenotypic	Shell VI_T5 Arenv/arprod/gsk1349572/ing111762/week48/drivers/mu_t_phen_acc_48.sas	Summary of Subject Accountability: Phenotype Available		24wk, 48wk
4.6.	CVW Phenotypic	Shell VI_T6 arenv/arprod/gsk1349572/ing114467/week48/drivers/ph_t_ot_sus_572ral.sas	Summary of Fold Change to DTG and LPV/RTV at Baseline and Time of Confirmed Virologic Withdrawal		24wk, 48wk
4.7.	CVW Phenotypic	Shell VI_T7 gsk1349572/ing111762/week48/drivers/ph_t_pss_shift_48.sas	Summary of Changes in Phenotypic Resistance (PSS_f) to Background ART Regimen at Time of Confirmed Virologic Withdrawal		24wk, 48wk

11.17.8. Health Outcomes

11.17.8.1. Tables

Health Outcome					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
HIV-Treatment Satisfaction Questionnaire					
5.1.	ITT-E	Shell HO_T1 gsk2619619/ing117172/week48/drivers/t_qs_indiv_locf.sas	Summary of HIV-Treatment Satisfaction Questionnaire Individual Item Scores	Modify program to use OC rather than LOCF & include all items from 14-item HIVTSQ. For Health Outcome SUMMARY tables use TU_FREQ	24wk, 48wk
5.2.	ITT-E	Shell HO_T2 gsk2619619/ing117172/week48/drivers/t_qs_indiv_locf.sas	Summary of HIV-Treatment Satisfaction Questionnaire Treatment Satisfaction Score		24wk, 48wk
5.3.	ITT-E	Shell HO_T3 gsk2619619/ing117172/week48/drivers/t_qs_indiv_locf.sas	Summary of HIV-Treatment Satisfaction Questionnaire Pain/Discomfort Satisfaction Item Score	Use Shell HO_T2. This is item 12 only.	24wk, 48wk
5.4.	ITT-E	Shell HO_T4	Summary of HIV-Treatment Satisfaction Questionnaire Change from Baseline in Individual Item Scores	Use Shell HO_T2	24wk, 48wk
5.5.	ITT-E	Shell HO_T5	Summary of HIV-Treatment Satisfaction Questionnaire Change from Baseline in Treatment Satisfaction Score	Use Shell HO_T2	24wk, 48wk
5.6.	ITT-E	Shell HO_T6	Summary of HIV-Treatment Satisfaction Questionnaire Change from Baseline in Pain/Discomfort Satisfaction Item Score	Use Shell HO_T2	24wk, 48wk

Health Outcome					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
5.7.	ITT-E	Shell HO_T7	Statistical Analysis of HIV-Treatment Satisfaction Questionnaire Change from Baseline in Treatment Satisfaction Score by visit – Repeated Measure Mixed Model Analysis		24wk, 48wk
5.8.	ITT-E	Shell HO_T8	Statistical Analysis of HIV-Treatment Satisfaction Questionnaire Change from Baseline in Treatment Satisfaction Score at Week 24/48 - Repeated Measures Mixed Model Analysis		24wk, 48wk
5.9.	ITT-E	Shell HO_T9	Summary of HIV-Treatment Satisfaction Questionnaire in Individual Item Scores Change	Use Shell HO_T1	48wk
5.10.	ITT-E	Shell HO_T10	Summary of HIV-Treatment Satisfaction Questionnaire in Treatment Satisfaction Score Change	Use Shell HO_T2	48wk
5.11.	ITT-E	Shell HO_T11	Summary of HIV-Treatment Satisfaction Questionnaire in Pain/Discomfort Item Score Change	Use Shell HO_T2	48wk
5.12.	ITT-E	Shell HO_T12	Statistical Analysis of HIV-Treatment Satisfaction Questionnaire in Treatment Satisfaction Score Change at Week 48	New output	48wk
Morisky Medication Adherence Scale – 8					
5.13.	ITT-E	Shell HO_T13	Summary of the Morisky 8-Item Medication Adherence Scale - Total Score		24wk, 48wk
5.14.	ITT-E	Shell HO_T14	Summary of the Morisky 8-Item Medication Adherence Scale - Adherence Level		24wk, 48wk
5.15.	ITT-E	Shell HO_T15	Statistical Analysis of the Morisky 8-Item Medication Adherence Scale – Adherence Level	New output	24wk, 48wk
Gastrointestinal Symptom Rating Scale					
5.16.	ITT-E	Shell HO_T16	Summary of Gastrointestinal Symptom Rating Scale – Individual Item Scores		24wk, 48wk

Health Outcome					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
5.17.	ITT-E	Shell HO_T17	Summary of Gastrointestinal Symptom Rating Scale - Diarrhoea Syndrome Score		24wk, 48wk
5.18.	ITT-E	Shell HO_T18	Summary of Gastrointestinal Symptom Rating Scale – Indigestion Syndrome Score		24wk, 48wk
5.19.	ITT-E	Shell HO_T19	Summary of Gastrointestinal Symptom Rating Scale Constipation Score		24wk, 48wk
5.20.	ITT-E	Shell HO_T20	Summary of Gastrointestinal Symptom Rating Scale - Abdominal Score		24wk, 48wk
5.21.	ITT-E	Shell HO_T21	Summary of Gastrointestinal Symptom Rating Scale – Reflux Score		24wk, 48wk
5.22.	ITT-E	Shell HO_T22	Summary and Statistical Analysis of Change from Baseline in Gastrointestinal Symptom Rating Scale - Diarrhoea Syndrome Score		24wk, 48wk
5.23.	ITT-E	Shell HO_T23	Summary and Statistical Analysis of Change from Baseline in Gastrointestinal Symptom Rating Scale – Indigestion Syndrome Score		24wk, 48wk
5.24.	ITT-E	Shell HO_T24	Summary and Statistical Analysis of Change from Baseline in Gastrointestinal Symptom Rating Scale Constipation Score		24wk, 48wk
5.25.	ITT-E	Shell HO_T25	Summary and Statistical Analysis of Change from Baseline in Gastrointestinal Symptom Rating Scale - Abdominal Score		24wk, 48wk
5.26.	ITT-E	Shell HO_T26	Summary and Statistical Analysis of of Change from Baseline in Gastrointestinal Symptom Rating Scale – Reflux Score		24wk, 48wk

11.17.9. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Study Population					
1.	All Subjects Screened	ES7	Listing of Reasons for Screen Failure	CS CORE	24wk, 48wk
2.	Randomised	Shell POP_L1 gsk2619619/ing117172/week48/drivers/sa_l_rand_notrt.sas	Listing of Subjects Randomised But Not Treated	CS CORE (related to 'Listing for exclusion from any population)	24wk, 48wk
3.	Randomised	TA1	Listing of Randomised and Actual Strata and Treatment Assignment	CS CORE	24wk, 48wk
4.	ITT-E	ES2	Listing of Reasons for Study Withdrawal	CS CORE	24wk, 48wk
5.	ITT-E	SD3	Listing of Study Treatment Discontinuation Record		
6.	ITT-E	BL1	Listing of Subjects for Whom the Treatment Blind Was Broken	CS CORE	24wk, 48wk
7.	ITT-E	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	CS CORE	24wk, 48wk
8.	ITT-E	DV2	Listing of Important Protocol Deviations	CS CORE	24wk, 48wk
9.	ITT-E	Shell POP_L2 gsk2619619/ing117172/week48/drivers/pd_l_protdev_expp.sas	Listing of Important Protocol Deviations Leading to Exclusion from the Per-Protocol Population	CS CORE	24wk, 48wk
10.	ITT-E	DM2	Listing of Demographic Characteristics	CS CORE	24wk, 48wk

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
11.	ITT-E	DM9	Listing of Race	CS CORE	24wk, 48wk
Efficacy					
12.	ITT-E	Shell EFF_L1 gsk2619619/ing117172/week48/drivers/l_eff_hivrna.sas	Listing of Qualitative and Quantitative Plasma HIV-1 RNA Data	Include the interpretation of whether the virus is detected or not ('Detected' or 'Not Detected') by the assay	24wk, 48wk RC
13.	ITT-E	Shell EFF_L2 gsk2619619/ing117172/week48/drivers/l_so_01.sas	Listing of Study Outcome (<50 c/mL) at Week X – Snapshot Analysis		24wk, 48wk
14.	ITT-E	Shell EFF_L3 gsk2619619/ing117172/week48/drivers/l_so_02.sas	Listing of Study Outcome (<400 c/mL) at Week X – Snapshot Analysis		24wk, 48wk
Safety					
15.	Safety	HIV_IP5	Listing of Investigational Product Exposure Data	CS CORE	24wk, 48wk RC
16.	Safety	HIV_IP5	Listing of Investigational Product Exposure Data – Mexican Subjects	CS CORE	EOS RC
17.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	CS CORE	24wk, 48wk RC
18.	Safety	AE8	Listing of All Adverse Events	CS CORE	24wk, 48wk RC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
19.	Safety	AE8	Listing of Adverse Events Potentially Related to Torsades de Pointes		24wk, 48wk RC
20.	Safety	AE8	Listing of Fatal Adverse Events	CS CORE	24wk, 48wk RC
21.	Safety	AE8	Listing of Fatal Serious Adverse Events		24wk, 48wk RC
22.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	CS CORE	24wk, 48wk RC
23.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product	CS CORE	24wk, 48wk RC
24.	Safety	AE2	Listing of Relationship of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	CS CORE	24wk, 48wk RC
25.	Safety	SAE Reasons AE14	Listing of Reasons for Considering as a Serious Adverse Event	CS CORE FDA	24wk, 48wk RC
26.	Safety	LB5	Listing of Clinical Chemistry Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern	CS CORE	24wk, 48wk RC
27.	Safety	LB5	Listing of Hematology Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern	CS CORE	24wk, 48wk RC
28.	Safety	UR2a	Listing of Urinalysis Data for Subjects with Abnormalities of Potential Clinical Concern	CS CORE	24wk, 48wk RC

11.17.10. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Study Population					
29.	All Subjects Screened	Shell POP_L3 gsk2619619/ing 117172/week48 /drivers/sa_l_po p.sas	Listing of Study Populations		24wk, 48wk
30.	All Subjects Screened	Shell POP_L4 gsk2619619/ing 117172/week48 /drivers/l_subre c_c.sas	Listing of Subject Recruitment by Country and Site Number		24wk, 48wk
31.	ITT-E	Shell POP_L5 gsk2619619/ing 117172/week48 /drivers/sa_l_vi sits.sas	Listing of Visit Dates		24wk, 48wk RC
32.	ITT-E	Shell POP_L6 gsk2619619/ing 117172/week48 /drivers/lb_l_he ptst.sas	Listing of Hepatitis Test Results		24wk, 48wk
33.	ITT-E	CDC3	Listing of CDC Classification of HIV Infection at Baseline		24wk, 48wk
34.	ITT-E	MH2	Listing of Current and Past Medical Conditions at Baseline		24wk, 48wk

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
35.	ITT-E	Shell POP_L7 gsk2619619/ing 117172/week48 /drivers/l_card_ risk.sas	Listing of Baseline Cardiovascular Risk Assessment Data		24wk, 48wk
36.	ITT-E	Shell POP_L8 gsk2619619/ing 117172/week48 /drivers/l_hist_c ardiac.sas	Listing of History of Cardiac Therapeutic Procedures		24wk, 48wk
37.	ITT-E	Shell POP_L9 gsk2619619/ing 117172/week48 /drivers/invp_l_ acct.sas	Listing of Investigational Product Accountability		24wk, 48wk RC
38.	ITT-E	CM2	Listing of Concomitant Medications	CS CORE	24wk, 48wk RC
39.	ITT-E	CM6	Listing of Relationship Between ATC Level 1, Ingredient and Verbatim Text		24wk, 48wk RC
40.	ITT-E	CA3	Listing of Prior Antiretroviral Therapy		24wk, 48wk
41.	ITT-E	CA5	Listing of Concomitant and Post-treatment Antiretroviral Therapy		24wk, 48wk RC
42.	ITT-E	CA5	Listing of Subjects with Changes in Background Antiretroviral Therapy		24wk, 48wk RC
43.	ITT-E	CA7	Listing of Relationship Between ATC Level 4, Combination, and Verbatim Text for ART		24wk, 48wk RC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Efficacy					
44.	ITT-E	Shell EFF_L4 gsk2619619/ing117172/week48/drivers/lb_cd4cc.sas	Listing of CD4+ Cell Count Data		24wk, 48wk RC
45.	ITT-E	HIV4	Listing of HIV-1 Associated Conditions		24wk, 48wk RC
46.	ITT-E	Shell EFF_L5 gsk1349572/ing111762/week48/drivers/ef_l_hv1rn_olpdvf.s	Listing of Viral Load over time for Subjects with Confirmed Virologic Withdrawal Criteria	Other Listing 71 from SAILING	24wk, 48wk
47.	ITT-E	Shell EFF_L6 gsk1349572/ing111762/week48/drivers/ef_l_hv1rn_olpdvf.s	Listing of Viral Load over time for Subjects with Confirmed Virologic Withdrawal Criteria During the Continuation Phase	Other Listing 71 from SAILING	24wk, 48wk RC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
48.	ITT-E	Shell EFF_L7 Listing 48 - gsk2619619/ing117172/week48/drivers/ef_l_cvw.sas Listing 77 - gsk2619619/ing117172/week48/drivers/mu_l_geno_resist.sas	Listing of Viral Load over time for Subjects with on-treatment virology results at non-CVWC timepoints	Use non-ICH listing 48 (for the format) and 77 (for the subjects to be included)	24wk, 48wk RC?
49.	ITT-E	Shell EFF_L8 gsk1349572/ing111762/week48/drivers/mu_t_vlcd4_pdvf.sas	Plasma HIV-1 RNA and CD4+ Cell Count at Confirmed Virologic Withdrawal Criteria	Use Table 12.60, update as a listing, update population and program name	24wk, 48wk RC?

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Safety					
50.	Safety	AE8	Listing of Non-Serious AEs of Mexican Subjects		EOS, RC
51.	Safety	AE8	Listing of SAEs of Mexican Subjects		EOS, RC
52.	Safety	AE8	Listing of SAEs of non-Mexican Subjects		EOS, RC
53.	Safety	PREG1a	Listing of Subjects Who Became Pregnant During the Study		24wk, 48wk RC
54.	Safety	LB5	Listing of Clinical Chemistry Data		24wk, 48wk RC
55.	Safety	LB5	Listing of Hematology Data		24wk, 48wk RC
56.	Safety	LB5	Listing of Laboratory Data for Subjects with Grade 3 or 4 Post-Baseline Emergent Toxicities	See for the shell arenv/arprod/gsk1349572/ing111762/week48/drivers/lb_l_maxaltbil.sas	24wk, 48wk RC
57.	Safety	LB5	Listing of Urinalysis Concentration Data		24wk, 48wk RC
58.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		24wk, 48wk RC
59.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	If a liver stopping event is reported	24wk, 48wk RC
60.	Safety	Shell SAFE_L1 gsk2619619/ing117172/week48/drivers/lb_l_maxaltbil.sas	Listing of Post Baseline Maximum ALT and Maximum Bilirubin		24wk, 48wk RC
61.	Safety	EG5	Listing of ECG Findings	Only collected for CV events	24wk, 48wk RC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
62.	Safety	VS4	Listing of Vital Signs		24wk, 48wk RC
63.	Safety	ABC_HSR _EXPO2	Listing of Abacavir Hypersensitivity Reaction Record - Exposure to Abacavir		24wk, 48wk RC
64.	Safety	ABC_HSR _DRUG2	Listing of Abacavir Hypersensitivity Reaction Record - Subject History of Drug Allergies		24wk, 48wk RC
65.	Safety	ABC_HSR COND2	Listing of Abacavir Hypersensitivity Reaction Record - Subject and Family Conditions		24wk, 48wk RC
66.	Safety	ABC_HSR _RASH2	Listing of Abacavir Hypersensitivity Reaction Record - Skin Rash Details		24wk, 48wk RC
67.	Safety	ABC_HSR _SYMP4	Listing of Abacavir Hypersensitivity Reaction Record - Symptoms		24wk, 48wk RC
68.	Safety	VS4	Listing of Abacavir Hypersensitivity Reaction Record - Vital Signs		24wk, 48wk RC
69.	Safety	ABC_HSR _SYMP6	Listing of Abacavir Hypersensitivity Reaction Record - Individual Symptoms and Diagnostic Category Assignments (Excluding Other Symptoms)		24wk, 48wk RC
70.	Safety	ABC_HSR _SYMP7	Listing of Abacavir Hypersensitivity Reaction Record - Individual Symptoms and Diagnostic Category Assignments (Other Symptoms)		24wk, 48wk RC
71.	Safety	LIVER5	Listing of Liver Event Results and Time of Event Relative to Treatment		24wk, 48wk RC
72.	Safety	LIVER6	Listing of Liver Event Information for RUCAM Score		24wk, 48wk RC
73.	Safety	LIVER7	Listing of Liver Biopsy Details		24wk, 48wk RC
74.	Safety	LIVER8	Listing of Liver Imaging Details		24wk, 48wk RC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
75.	Safety	MH2	Listing of Past and Current Liver Disease Medical Conditions		24wk, 48wk
76.	Safety	LB5	Listing of Laboratory Data from Liver Event Follow-Up		24wk, 48wk RC
Virology					
77.	ITT-E	Shell VI_L1 gsk1349572/ing111762/week48/drivers/mu_l_geno_all.sas	Listing of All Genotypic Data	Baseline and on study genotypes are MAINLY Monogram, but some Q2 will be in there. We need to note when it is from Q2 versus Monogram to assist with potential subtle differences in how the resistance data is annotated and provided	24wk, 48wk RC
78.	ITT-E	Shell VI_L2 gsk1349572/ing111762/week48/drivers/ph_l_pheno_all.sas	Listing of All Phenotypic Data		24wk, 48wk RC
79.	All Subjects Screened	Shell VI_L3 gsk1349572/ing111762/week48/drivers/mu_l_geno_all.sas	Listing of All Screening Genotype Data from Quest	New (study specific)	24wk, 48wk

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
80.	ITT-E	Shell VI_L4 gsk1349572/ing111762/week48/drivers/mu_t_virology_pdvf	Listing of Genotypic and Phenotypic Data for Subjects with Confirmed Virologic Withdrawal Criteria	Use T12.59 from SAILING. Update as a listing and also title and population Potentially different assays,phenotypic assay for RT PRO and Integrase. Can we identify this in the listing	24wk, 48wk RC
81.	ITT-E	Shell VI_L5 gsk1349572/ing111762/week48/drivers/mu_t_virology_pdvf.sas	Listing of Genotypic and Phenotypic Data for Subjects with Confirmed Virologic Withdrawal Criteria During the Continuation Phase	Use T12.59 from SAILING. Update as a listing and also title and population	24wk, 48wk C
82.	ITT-E	Shell VI_L6 gsk1349572/ing111762/week48/drivers/mu_t_virology_last	Listing of Genotypic and Phenotypic Data for Subjects with on-treatment virology results at non-CVW timepoints	Use T12.59 from SAILING. Update as a listing and also title and population	24wk, 48wk RC
83.	ITT-E	Shell VI_L7 gsk1349572/ing111762/week48/drivers/ph_l_pheno_bg_pdvf.sas	Subject Level Summary of Key Virologic Data for Subjects with Confirmed Virologic Withdrawal or Last On-treatment VL >400 c/mL	As in Table 12.62 (SAILING) but add columns for DTG FC, LPV FC, IN substitutions, Major PI mutations, mutations, Major NRTI, Major NNRTI mutations; flag for CVW/Last VL >400.	

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
Health Outcome Listings					
84.	ITT-E	Shell HO_L1 gsk2619619/ing 117172/week48 /drivers/l_hivtre at_sat.sas	Listing of HIV-Treatment Satisfaction Questionnaire in Individual Item Scores and Treatment Satisfaction Score	Use TU_LIST for all Health Outcome Listings Change SAS program to exclude Lifestyle Ease Score and General Satisfaction Clinical Score	24wk, 48wk
85.	ITT-E	Shell HO_L2 gsk2619619/ing 117172/week48 /drivers/l_hivtre at_sat.sas	Listing of HIV-Treatment Satisfaction Questionnaire in Individual Item Scores Change and Treatment Satisfaction Score Change	Modify program to use HIVTSQc	48wk
86.	ITT-E	Shell HO_L3	Listing of Morisky 8-Item Medication Adherence Scale Individual Items, Total Score and Adherence Level	New output but can use TSQ listing SAS code – Shell HO_L1	24wk, 48wk
87.	ITT-E	Shell HO_L4	Listing of Gastrointestinal Symptom Rating Scale – Individual Item Scores	New output but can use TSQ listing SAS code – Shell HO_L1	24wk, 48wk
88.	ITT-E	Shell HO_L5	Listing of Gastrointestinal Symptom Rating Scale - Syndrome Scores	New output but can use TSQ listing SAS code – Shell HO_L1	24wk, 48wk

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable & phase [Priority]**
89.			Patient profiles for subjects meeting protocol defined liver stopping criteria,	Example in /arenv/arprod/gsk1349572/ing_idmc/interim1/drivers/dm_l_patproflist2.sas or /arwork/…/<study>/profiles/profile.sas Include: Investigator, country, tmt, sex, DOB, age, race, medical history, IP start and end date, reasons for discontinuation, AE, conmeds, prior ART, labs, viral loads, vital signs.	24wk, 48wk
90.			Patient profiles for subjects with virological failures		24wk, 48wk