Statistical Analysis Plan

Study ID: 212483

Official Title of Study: A Phase IIb, Randomized, Double-blind, Parallel-group Study to Assess the Efficacy, Safety, Tolerability, and Resistance Profile of GSK3640254 in Combination With Dolutegravir Compared to Dolutegravir Plus Lamivudine in HIV-1 Infected, Treatment-naïve Adults

NCT ID: NCT04900038

Date of Document: 19 May 2023

Statistical Analysis Plan for Interventional Studies

Full SAP Text (through to EoS)

Sponsor Name: ViiV Healthcare UK Limited ("ViiV") is the Sponsor of the Clinical Trial. GlaxoSmithKline Research & Development Limited (GSK) on behalf of ViiV Healthcare UK Limited is outsourcing full service to Syneos Health

Protocol Number: 212483
Protocol Title: A Phase IIb, randomized, double-blind, parallel-group study to assess the efficacy, safety, tolerability, and resistance profile of GSK3640254 in combination with dolutegravir compared to dolutegravir plus lamivudine in HIV-1 infected, treatment naïve adults
Acronym: DYNAMIC

Protocol Version and Date: (DD-Mmm-YYYY): Amendment 03, 11-Aug-2022

Syneos Health Project Code: 7023653

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)

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ViiV Healthcare and GlaxoSmithKline Approval

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	01-Dec-2022	PPD	Initial Release Version
2.0	17-May-2023	PPD	Updates for End of Study analysis

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ART	Anti-Retroviral Therapy
BMI	Body Mass index
c/mL	Copies / mL
DTG	Dolutegravir
CCI [redacted]	
IA	Interim Analysis
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ITT-E	Intent-to-Treat Exposed
LPLV	Last Patient Last Visit
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PK	Pharmacokinetics
PP	Per-Protocol
PPS	Per-Protocol Set
PDVF	Protocol Defined Virologic Failure
CCI [redacted]	
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
sFTP	Secure File Transfer Protocol
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SRT	Safety Review Team

Abbreviation	Description
SYNH	Syneos Health
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
VL	Viral Load
VOI	Visit of Interest
EoS	End of Study

2. Purpose

The purpose of this statistical analysis plan (SAP) is to describe planned analyses and output to be included in the Clinical Study Reports for Protocol 212483 and to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This document will cover statistical analysis plan intended to describe the efficacy, safety, virology and PK required through to EoS.

An addendum to this SAP will be developed at a later stage to convey the content of the continued access phase.

2.1. Responsibilities

Syneos Health (SYNH) will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings.

2.2. Planned Analyses

2.2.1. Interim Analyses

2.2.1.1. Week 12 - IDMC Analysis

An independent data monitoring committee (IDMC) will conduct an interim analysis. Full details of this methods, timing, decision criteria and operating characteristics are contained in the IDMC charter document "208379 and 212483 IDMC Charter version 2.0 final" and the IDMC SAP, which also describes the tables, figures, and listings (TFL) outputs which will be presented for different IDMC scenarios.

2.2.2. Final Analyses

2.2.2.1. Week 24 - Primary Analysis

The primary analysis will be conducted to evaluate the efficacy, safety and tolerability of GSK3640254 + DTG when all participants have completed their Week 24 visit or discontinued.

Treatment code would be unblinded at Week 24, once after all criteria for unblinding the randomization codes have been met.

2.2.2.2. End of Study Analysis

The end of study analysis will be conducted after all participants have reached end of study visit due to early termination or discontinued.

Each of these analyses will be performed after the completion of the following sequential steps:
All participants have completed the end of study visits due to early termination.
All required database cleaning activities have been completed database lock (DBL) have been declared by Data Management.

3. Statistical Hypotheses

The primary analysis of the study is designed to investigate the efficacy, safety, tolerability and resistance of three doses (100 mg, 150 mg, and 200 mg) of GSK3640254 + Dolutegravir (DTG), relative to DTG/ lamivudine (3TC) for 24 week. Although no formal statistical analysis will be carried out in this study, Bayesian analyses will be conducted to evaluate the probability that the Week 24 response rate, defined as the proportion of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) as calculated by the FDA snapshot algorithm, of at least one dose of GSK3640254+DTG have comparable efficacy to the reference treatment using a 12% margin. A positive sign of efficacy will be achieved if any GSK3640254+DTG dose has a high posterior probability (e.g., ≥75%) of being within the 12% margin.

4. Study Objectives

Objectives	Endpoints
Primary	
• To evaluate antiviral efficacy of GSK3640254 + DTG, relative to DTG/3TC at Week 24 in HIV-1-infected, ART-naïve participants	• Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 using the FDA snapshot algorithm
Secondary	
• To evaluate the antiviral activity of GSK3640254 + DTG relative to DTG/3TC	• Absolute values and changes from baseline in HIV-1 RNA through Weeks 24 • Absolute values and changes from baseline in CD4+ T-cell counts through Weeks 24
• To evaluate safety and tolerability of GSK3640254 when given in combination with DTG, relative to DTG/3TC	• Frequency of SAEs, Deaths and AEs leading to Discontinuation through Weeks 24 • AEs of special interest (AESIs) through Weeks 24
• To assess the development of viral resistance to GSK3640254+DTG and other on-study ART in participants experiencing virologic failure	• Changes in genotypic and/or phenotypic profiles of virus compared to baseline
• To assess the steady-state exposure of GSK3640254 when given in combination with DTG	• The steady-state plasma PK parameters of GSK3640254+DTG will be assessed based on Sparse PK sampling
Exploratory	

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

5. Study Details/Design

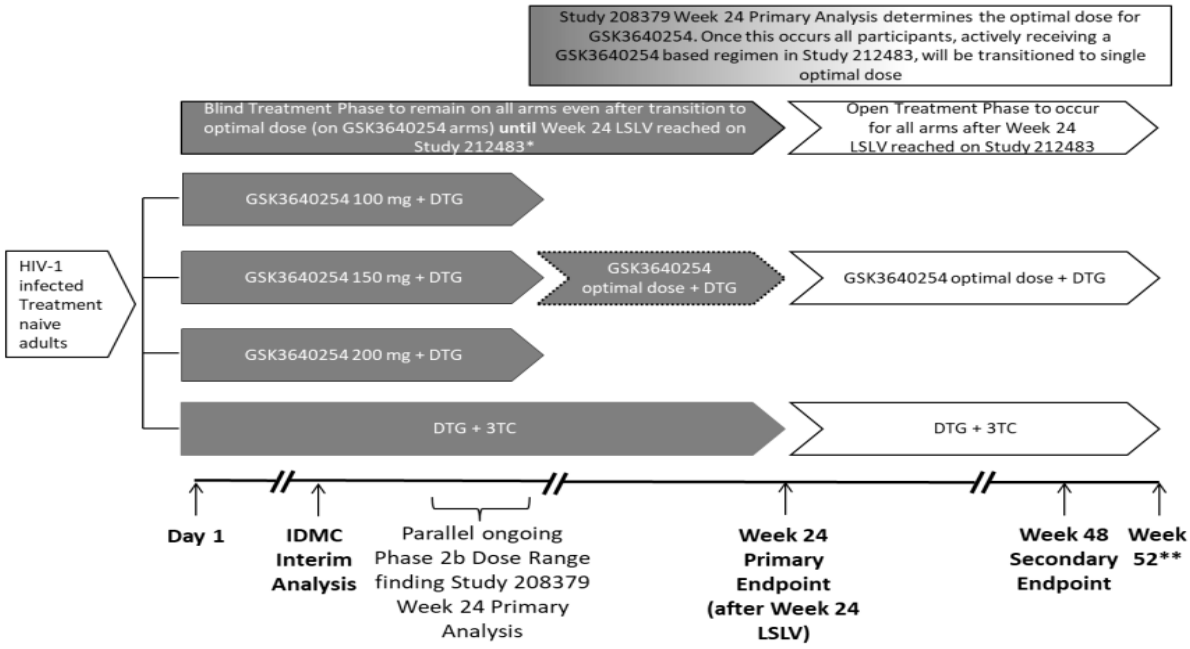
5.1. Brief Description

Study 212483 is a Phase IIb, randomized, multicenter, double-blind, active-controlled, parallel group study to be conducted in approximately 80 ART-naïve adults living with HIV-1. Participants will be stratified by screening plasma HIV-1 RNA, by <100,000 c/mL or ≥100,000 c/mL and randomized to one of the three doses of blinded GSK3640254 (100, 150, or 200 mg) or a reference arm of blinded 3TC – each in combination with open label DTG.

The study will include:

- A Screening Phase to a maximum of 30 days
- A Double-blind Randomized Phase (first participant Day 1 to last participant Week 24)
- An Open-label Randomized Phase (at least last participant Week 24 to last participant Week 52)
- Continued Access Phase

Another Phase 2b study, 208379 (DOMINO), has been ongoing since November 2020, a dose range finding trial, where this study activity may serve as a trigger for IDMC activities as well as adopting optimal dose selected from DOMINO into DYNAMIC study.



*Participants in this study (212483) reaching Week 24 before selection of the GSK3640254 optimal dose in Study 208379 will continue on their original GSK3640254 dose until the optimal dose is known (expected prior to the overall study's Week 24 primary endpoint). Treatment allocation will remain blinded until after the Week 24 primary endpoint analysis, then will become open label.

**Participants on GSK3640254 arms may continue to receive study medication beyond their individual Week 52 visit. Based on the above sequence of events and when each participant reaches Week 52 relative to the Week 24 primary endpoint analysis, participants on GSK3640254 arms may receive: double blind non-optimal dose, double blind optimal dose, and/or open label optimal dose. Participants on the reference arm may continue to receive DTG + 3TC only if they reach their individual Week 52 visit during the Blind Treatment Phase. After the Open Treatment Phase starts, DTG + 3TC will be discontinued for all participants who have completed Week 52. Please see protocol Section 6.6 for full details.

5.1.1. Study Completion

Element	Reporting Detail
General	Participants are considered to have completed the study if they remain on therapy (i.e.,have not permanently discontinued IP) and satisfy one of the following: • Randomly assigned to either treatment group, completed the blinded treatment phase and open treatment phase including the Week 52 visit, and did not enter Continued Access Phase • Randomly assigned to either treatment group, completed the blinded treatment phase and open treatment phase including the Week 52 visit, and enter Continued Access Phase (defined as remaining on study until commercial supplies of GSK3640254 become locally available or development of GSK3640254 is terminated). • Randomly assigned to either treatment group, completed the blinded treatment phase and but did not enter open treatment phase including the Week 52 visit because development of GSK3640254 is terminated.

5.2. Patient Selection

5.2.1. Inclusion Criteria

The inclusion criteria are listed in section 5.1 of the protocol.

5.2.2. Exclusion Criteria

The exclusion criteria are listed in section 5.2 of the protocol.

5.3. Determination of Sample Size

Approximately 160 participants will be screened to achieve approximately 80 randomly assigned to study intervention for an estimated total of 20 evaluable participants per GSK3640254 + DTG and DTG/3TC arm. However, as a result of the potential impact of the parallel Phase 2b trial, Study 208379, the enrolment of Study 212483 may be adaptive resulting in no more than 30 participants originally randomized to any treatment arm. The planned sample size of approximately 20 participants per active arm and approximately 20 participants assigned to the reference arm is based on the primary efficacy endpoint of FDA Snapshot response rate at Week 24 (proportion of participants with plasma HIV-1 RNA <50 c/mL).

Considering the small sample size of the study, response rate 90% (N=18) is used for the reference arm, and a response rate of 78% on the optimal dose, the probability of declaring positive sign of efficacy is approximately 27.5%. Given the stage of this phase 2b study and the relatively small sample size of each

arm, this is considered acceptable. Conversely, assuming a response rate of 90% on the optimal dose, the probability of declaring a positive sign of efficacy would be 78.4%.

5.4. Treatment Assignment and Blinding

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS).

To minimize bias, all treatment arms (GSK3640254) will be blinded to the research participants and all study personnel during the study through Week 24. After Week 24 in DYNAMIC and the selection of the optimal dose in DOMINO, the DYNAMIC study will be unblinded, and the open-label randomized phase will begin.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK and ViiV Healthcare policy.

The SYNH blinded team will include a Lead Biostatistician, SDTM programmers, ADaM/TFL programmers as well as a Senior Reviewing Statistician. A separate unblinded team will work independently of the blinded team to receive, review, and manage the unblinded data. The unblinded team including an unblinded statistician, an unblinded senior review statistician, and unblinded programmers do not have any day-to-day roles in the conduct of the study.

Any IDMC will occur while the study is still blinded. Unblinded outputs will be presented in a masked fashion for treatment groups (i.e., treatment groups labelled as A, B, C, D, where the order is random). Further details of the roles and responsibilities of the unblinded statistician are outlined in the IDMC Charter.

The blinded team will develop and validate the SAS programs necessary for analysis on the blinded data. Once validated, the unblinded programming team members will run the SAS programs on the unblinded study data in a secure, access-restricted area. The unblinded statistician will review the outputs produced by the unblinded team. Unblinded outputs will be distributed via SYNH Secure File Transfer Protocol (sFTP) in an unblinded area, where only unblinded members have access.

Data with the potential to unblind, i.e., PK concentration data, will be available to the blinded team only in a blinded fashion. Any potentially unblinding information will be masked prior to hand-off to the blinded team.

5.5. Administration of Study Medication

	GSK3640254	GSK3640254 Placebo	DTG	3TC	3TC Placebo	3TC[a]
Intervention Name	GSK3640254	Placebo to match GSK3640254	Tivicay (The clinical label will state Dolutegravir 50mg to match the SPC)	3TC (The clinical label will state Lamivudine 300mg)	3TC Placebo (The clinical label will state Placebo to match Lamivudine 300mg)	3TC (The clinical label will state Lamivudine 300mg)
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Capsule	Capsule	Tablet
Unit Dose Strength(s)	25 mg, 100 mg	N/A	50mg	300mg	N/A	300mg
Dosage Level(s)	Variable depending on dose	Variable depending on dose	One tablet per day	One capsule per day	One capsule per day	One tablet per day
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Background	Comparator	Placebo	Comparator
IMP and NIMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and Labeling	32 tablets per HDPE bottle, labelled per country requirement	32 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement	32 capsules per HDPE bottle, labelled per country requirement	32 capsules per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement

[a] 3TC (Lamivudine 300mg) tablets for the Open Label phase will not be over-encapsulated, the existing commercial pack presentation (with a clinical label) will be supplied.

5.6. Study Procedures and Flowchart

Table 1:Schedule of Assessments

Procedures[1]	Screening (up to 30 days before Day 1)	Intervention Period[2]														Continued access phase[4]	Early Discontinuation/withdrawal	Follow- up[5]
		Week																
		Day 1 (Baseline)	2	4	8	12	16	20	24	28	32	36	40	44	48	52[3]	Every 12 weeks after Week 52	
Clinical and Other Assessments																		
Informed consent[6]	X														X			
Inclusion and exclusion criteria	X	X																
Demography	X																	
Prior ARV history to ensure naïve status	X																	
Medical history[7]	X																	
Height, weight (W) and BMI[8]	X	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (F=Full, T=Targeted)[10]		F					T		T						T		T	
CDC HIV-1 Classification[11]	X	X																
HIV-associated conditions[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia Suicidality Severity Rating Scale (C-SSRS)[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence review[14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event (AE)/SAE assessments	SAE Only	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																		

Procedures[1]	Screening (up to 30 days before Day 1)	Intervention Period[2]														Continued access phase[4]	Early Discontinuation/withdrawal	Follow- up[5]
		Week																
		Day 1 (Baseline)	2	4	8	12	16	20	24	28	32	36	40	44	48	52[3]	Every 12 weeks after Week 52	
CCI [redacted]																		
Laboratory Assessments																		
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
T-cell Lymphocyte subset	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for storage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for Geno/Phenotypic Resistance Assays[17]	X	X		X	X	X	X	X	X	X	X	X	X	X	X			X
Clinical chemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
PT/INR (For Child-Pugh)	X																	
Fasting lipids and glucose[18]	X	X				X			X						X		X	
Urine Drugs of Abuse panel[19]	X																	
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pregnancy test for POCBP only[20]	S	U/S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, Anti-HBs, and reflex HBV DNA	X																	
HCV antibody and reflex HCV RNA	X																	
Rapid Plasma Reagin (RPR)	X																	
Pharmacokinetics – Sparse[21]			X	X	X	X			X						X			

Procedures[1]	Screening (up to 30 days before Day 1)	Intervention Period[2]															Continued access phase[4]	Early Discontinuation/withdrawal	Follow- up[5]
		Day 1 (Baseline)	Week																
			2	4	8	12	16	20	24	28	32	36	40	44	48	52[3]	Every 12 weeks after Week 52		
Optional Genetics sample[22]		X																	
Study Treatment																			
Randomization		X																	
IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X	X
Dispense IP		X		X	X	X	X	X	X	X	X	X	X	X	X		X[23]		
IP accountability (pill counts)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X	

Abbreviations: BMI: Body mass index; CDC: Center for Disease Control and Prevention; HIV: Human immunodeficiency virus; CCI RNA: Ribonucleic Acid; POCBP: Participant of Childbearing Potential; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C Virus; IVRS/IWRS: Interactive Voice/Web Response System

1. Order of Assessments (pre-dose): C-SSRS – CCI – Vital Signs – Blood Draws (see notes in Section 8.4 regarding order for blood draw and CCI during the Week 2 visit)
2. The acceptable window around any visit, Week 4 and beyond, is ± 2 days. Participant must come in no later than +2 days of the visit windows or participant will run out of drug supply. If, due to unforeseen circumstances, a participant is unable to attend a visit during the visit window, measures for ensuring continued antiretroviral treatment and safety monitoring of the participant (e.g., those described in Section 10.11 for missed visits due to COVID-19), should be discussed and agreed with the Sponsor before implementation.
3. Participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, occurring prior to Week 52.
4. Participants who meet the criteria to be offered continued access to study treatment after Week 52 (see Section 6.6) will take part in the Continued Access Phase. Any participant who discontinues study treatment while in the Continued Access Phase for any reason, will attend withdrawal and follow-up visits.
5. See Section 4.1.3.
6. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility including review of additional assessments performed at Day 1. Consent for the continued access phase of the study must be obtained from the patient before or at their Week 48 visit, to allow additional medication to be allocated and dispensed at their Week 52 visit.

7. Medical History includes substance usage and the Medical Conditions listed in Exclusion Criteria in Section 5.2, as well as assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), and, in particular, but not limited to, cardiac, psychiatric, renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders including current medical conditions.
8. See Section 8.2.1.1.
9. See Section 8.2.2.
10. See Section 8.2.1.
11. See Section 10.10.
12. The Concomitant Medication review at Screening includes those listed in Section 6.8 to be considered relative to dosing requirements.
13. On Day 1, participants will provide response to the eC-SSRS Baseline form ***prior to*** the RAMOS task of Randomization. The eC-SSRS will be in electronic format, responses provided by participants either by phone or computer, whether they are in clinic or if they are remote (virtual visits). Participants can complete the eC-SSRS ±7 days from each visit post-randomization. See Section 8.2.6.
14. Adherence review includes pill count, review of any recorded missed doses, and a conversation about other possible missed doses if the pill count does not match those recorded and/or verbally reported.

CCI

16. If there are COVID-19 impacts that restrict the ability for a participant to come to the clinic for the day-long visit at Week 2, then, at the least, all participants should attend the clinic visit for the collection of HIV-1 RNA and as many of the CCI as possible.
17. See Section 7.1.1. Unused plasma samples collected for the potential need of resistance testing will enter long-term storage and are then included in the pool of samples that can be used for further research, if participant has consented.
18. An overnight fast is preferred prior to visits that include lipid assessments, but a minimum of 6 hours is acceptable.
19. Also to be done for any Grade 3-4 Psychiatric AE. See Section 8.2.6.
20. At Screening, and for POCBP only, sites will submit serum for FSH and Estradiol, and for Pregnancy testing. On Day 1, in addition to the serum sample sent to the central lab, a urine pregnancy test will be done in the clinic to confirm negative status prior to IP administration. If the urine test result is ambiguous, the site should await the results of the Day 1 serum test before study treatment can be initiated. On Treatment, a blood sample will be collected at each visit for serum pregnancy testing. Urine pregnancy tests will be done every 4 weeks at home, only if virtual visits occur (results need to be reported to the site). Any ambiguous urine result will need to be retested in serum. S=serum, U=urine
21. See Section 8.4 for details.
22. A separate genetics ICF is required.
23. If a participant is granted continued access to study treatment while the study is still in the Double-blind Treatment Phase, they will be required to return every 4 weeks to collect new study treatment. No other procedures or assessments will be performed at those dispensing visits.

6. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprises Screened for inclusion in the study, including screen-failures. • This population will be based on the treatment to which the subject was randomized. Screen-failures will be categorized as "Non-randomized".	• Study Population
Randomized	• Any participant who has been randomized to study intervention (for this study, this means a randomization number was assigned), whether or not the participant ever took a dose of study medication. • Participants will be analysed according to the randomized treatment regardless of what treatment was actually received	• Study Population
Safety	• All randomized participants who were exposed to study intervention with the exception of any participants with documented evidence of not having consumed any amount of study intervention • This population will be analysed according to the actual treatment the participant received. The safety population will be the primary population for safety analyses.	• Safety
Intent-To-Treat Exposed (ITT-E)	• All randomized participants who received at least one dose of study treatment. • Participants will be analysed according to the randomized treatment regardless of what treatment was actually received	• Study Population • Efficacy
Per-Protocol (PP)	• This population will consist of subjects in the ITT-E Population except for Important protocol deviations designated as exclusions from the analysis population. • This population will be based on the treatment to which the subject was randomized. • Protocol deviations before a specified analysis timepoint that would exclude participants from the PP population are defined in Section 8.3 (Protocol Deviations) and Appendix 1: Exclusions from Per Protocol Population). E.g., a subject with an important protocol deviation between week 24 would not be excluded due to this deviation from week 24 PP population but would be excluded from PP population.	• Efficacy (Sensitivity analysis)

Population	Definition / Criteria	Analyses Evaluated
Sparse Pharmacokinetic (Sparse PK)	• The pharmacokinetic (PK) population will include all participants who receive GSK3640254+DTG, undergo sparse PK sampling during the study, and provide evaluable GSK3640254+DTG plasma concentration data. Participants in this population will be included in the PK analysis. Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded.	PK
Viral Genotypic	• Comprise of all subjects who receive at least one dose of study treatment who have available On-treatment genotypic resistance data. • This population will be based on the treatment to which the subject was randomized	• Viral Genotypic
Viral Phenotypic	• Comprise of all who receive at least one dose of study treatment who have available On-treatment phenotypic resistance data. • This population will be based on the treatment to which the subject was randomized	• Viral Phenotypic
PDVF	• All subjects in the ITT-E population who met the PDVF criteria defined in the protocol. • PDVF is defined as any of the following (and confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between two and four weeks (approx.) after the initial suspected virologic failure sample): • Decrease from Baseline (Day 1) in plasma HIV-1 RNA of <1.0 log10 c/mL unless plasma HIV-1 RNA is <200 c/mL by Week 12; • Confirmed plasma HIV-1 RNA levels ⩾200 c/mL at or after Week 24 • Plasma HIV-1 RNA ⩾50 c/mL on repeat testing of Week 24 results and prior to Week 28. • Confirmed plasma HIV-1 RNA ⩾200 c/mL after confirmed consecutive plasma HIV-1 RNA <50 c/mL	• Efficacy

7. General Aspects for Statistical Analysis

7.1. General Methods

- SAS® version 9.4 or higher to be used
- All TLFs will be produced using the Courier New font, size 10
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum and for some outputs geometric mean would also be used. Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. Categorical variables will be summarized using number of observations (n), frequency and percentages of participants.
- All relevant participant data will be included in listings. All participants' data entered into the database will be included in participant data listings.
- For output name, for table it would start with "t_", eg t_01-01 or t_01_01 and for figure it starts with f_. For listing, if listing is based on ICH listing, it should start with li_, eg, li_02_51, and if it is from non-ICH listing it should start with lo_, eg, lo_02_61.

7.2. Baseline Definitions

First dose date is defined as the date of the first dose of study intervention received after randomization in the double-blind randomized phase (Day 1 to Week 24). Last dose date is defined as the date of the last dose of study intervention. For participants ongoing at the time of analysis, the last dose date will be the most recent start/end date of exposure collected in the database for that participant.

For all the endpoints, unless otherwise stated, baseline is defined as the latest non-missing value prior to first dose of treatment according to date and time including unscheduled visits. Baseline data points are expected to come from the Day 1 visit. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Safety			
CCI [redacted]			
Vital Signs	X	X	Day 1 (Pre-Dose)
Laboratory Assessments	X	X	Day 1 (Pre-Dose)
Efficacy			
HIV-1 RNA/ CD4+ T cell	X	X	Day 1 (Pre-Dose)
Virology			

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Genotypic/ Phenotypic	X	X	Day 1 (Pre-Dose)

CCI [redacted]

On Day 1 three readings of blood pressure and pulse will be taken. The first reading should be rejected. The average of the second and third readings (as recorded in the CRF) will serve as baseline.

For Genotypic and Phenotypic data, Day 1 visit data will serve as baseline, otherwise, baseline will be set to missing.

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

Study day is defined as (event date – first dose date + 1) if event date >= first dose date; study day is defined as (event date – first dose date) if event date < first dose date. That is, the date of first dose represents study day 1.

Demographic definitions include

Age
• For all subjects, the 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.

- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536
- Body Mass Index (BMI) (kg/m^2) = Weight(kg)/[Height(m)]^2

7.3. Missing Data

In any efficacy analysis applying the Snapshot algorithm, participants without HIV-1 RNA data in the assessment window for the visit of interest (due to missing data or discontinuation of study intervention prior to the visit window) are classified as either 'HIV-1 RNA ≥50 c/mL' or 'No Virologic Data'. For full details of the Snapshot algorithm see Appendix 15.4.4.

For handling of missing and partial dates for other assessments, please refer (Appendix 15.5.2)

7.4. Visit Windows

The Snapshot visit windows are used as part of the Snapshot algorithm to determine a participant's category (see Appendix 15.4.4). Snapshot analysis windows apply only to VL data that is on-treatment. Apart from Weeks 24, the window size is one-half the duration of time between study visits per protocol.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window (Days)		Analysis Timepoint	Window Weeks
			Beginning Timepoint (including)	Ending Timepoint (including)		
Snapshot	All	Day 85	Day 71	Day 98	Week 12	10-14
Snapshot	All	Day 169	Day 127	Day 210	Week 24	18-30

Other analyses Sets (e.g. lab) will use analysis windows ½ the distance between the previous and subsequent timepoint.

Please refer to Appendix 2 for visit windowing criteria for other analyses.

7.5. Multicenter Studies

In this multicentre global study, enrolment will be presented by country and investigative site. For purposes of efficacy analyses, all sites are assumed to be exchangeable and there will be no site or country level adjustment. Therefore, no by-center analyses are planned. Data will be summarized in an aggregate fashion.

7.6. Examination of Covariates, Other Strata and Subgroups

7.6.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Randomization Strata using Baseline Values	The randomization is stratified by factors which are assessed using screening values. The baseline categories are considered to be more relevant, hence the randomization strata are re-derived using baseline values and will be referred to as the analysis strata. The strata is as follows: Screening HIV-1 RNA (<100,000 copies/mL or >=100,000 copies/mL)

7.6.2. Examination of Subgroups

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

- If the percentage of participants 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.

- Descriptive summaries of subgroups will only include subjects with non-missing data. The number of subjects with non-missing data for each subgroup will be displayed in the table (n) and be used as the denominator in percent calculations.

Subgroup	Categories
CCI	[redacted]

7.6.3. Multiple Comparisons and Multiplicity

The study is designed to evaluate the efficacy primarily on the basis of antiviral activity and tolerability in conjunction with immunological response, safety, and pharmacokinetic measures and is not designed to evaluate formal statistical hypotheses. Hence, adjustments for multiplicity are not applicable.

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[redacted]

8.2. Subject Eligibility

Inclusion/exclusion criteria definitions and Inclusion/exclusion criteria violations will also be listed by patient for screened set.

8.3. Protocol Deviations

Protocol deviations will be identified periodically throughout the trial following the 'Protocol Deviation and Non-compliance Management Plan' (Syneos Health SOP and WI, 3101 and 3101.W02). Final definition of protocol deviations and categorization into Not Important / Important will be performed in the Blinded Data Review Meeting (BDRM) prior to database lock and unblinding.

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, dosing, and sampling procedures or patient assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the principal investigator and the study statistician, and finalized before database lock during the BDRM. Also, the determination whether an important protocol deviation has an impact on the assessment of the primary efficacy which result in exclusion of subjects from analysis population will be finalized in the BDRM following SOP 3911.All protocol deviations (Not important and Important) observed during the conduct of the study will be listed. Important protocol deviations (patients with at least one important PD overall and split by PD category will be summarized by treatment group for all ITT-E participants.

Please refer Appendix 1 for important PDs leading to exclusion from PP.

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[redacted]

CCI

[redacted]

8.5. Smoking and Alcohol History

Smoking and alcohol history will be summarized using standard descriptive statistics and listed for all patients for the ITT-E set patients.

8.6. Medical History

Current and Past medical history will be summarized in separate tables for the ITT-E set presenting the number and percentages of patients within each preferred term (PT) grouped by the system organ class (SOC), pre-printed in eCRF.

8.7. Prior and Concomitant Medication

The WHO Drug, March 2021, B3 will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

The use of concomitant medications will be summarized by the number and percentage of patients for the ITT-E set patients. If a patient takes a specific medication multiple times or takes multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class.

Prior and concomitant medications will be listed for all patients in the ITT-E population.

8.8. Treatment Compliance

. Treatment Compliance

- Treatment compliance will be calculated based on the formula:
  Treatment Compliance = Number of Actual Doses*100 / (Planned Treatment Duration in Days * Frequency)
- Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated.
- Planned treatment duration will be defined according to the endpoint analysed.

Endpoint	Planned Treatment Duration
Week 24 Snapshot (Primary)	24 weeks

9. Efficacy

9.1. Primary Efficacy Analysis

The primary analysis of the study is designed to investigate the antiviral activity of three doses (100 mg, 150 mg, and 200 mg) of GSK3640254 in combination with Dolutegravir (DTG), relative to DTG/lamivudine (3TC) at 24 weeks. To achieve this objective, Bayesian analyses will be conducted to evaluate the probability that the Week 24 response rate, defined as the proportion of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) as calculated by the FDA snapshot algorithm, of at least one dose of GSK3640254+DTG has comparable efficacy to the reference treatment using a 12% margin. A positive efficacy decision will be made if any GSK3640254+DTG dose has a high posterior probability (e.g., ≥75%) of being within the 12% margin.

9.1.1. Primary Endpoint

The primary efficacy endpoint is the binary outcome indicating the virologic category of plasma HIV-1 RNA <50 copies/mL at Week 24 using the FDA Snapshot algorithm (See Appendix 15.4.4). The other Snapshot outcomes (HIV-1 RNA ≥50 copies/mL and no virologic data at Week 24 Window) will be collapsed into a single category for the analysis (non-response category).

9.1.2. Summary Measure

For each dose of GSK3640254+DTG the following Bayesian statistics will be provided:

- The number and proportion of subjects with plasma HIV 1 RNA <50 copies/mL at Week 24 using the snapshot algorithm.
- Summary statistics of the posterior distribution of response rate for the specified dose including:
    - Mean, median, and mode of posterior distribution of response rate for specified dose.
    - 95% highest posterior density credible interval of response rate for specified dose.

For the DTG/3TC arm (control arm) the following Bayesian statistics will be provided:

- The number and proportion of subjects with plasma HIV 1 RNA <50 copies/mL at Week 24 using the snapshot algorithm
- Summary statistics of the posterior distribution of response rate for the control including:
    - Mean, median, and mode of posterior distribution of response rate.
    - 95% highest posterior density credible interval of response rate.
- Posterior Probability that response rate of the specific GSK3640254+DTG dose is greater than the DTG/3TC arm response rate -12%. That is:
    - Posterior Pr(Response rate GSK3640254+DTG XX mg – Response Rate DTG/3TC) > -0.12

  This posterior probability will be compared to 75% to determine positive sign for efficacy.

Treatment comparisons will be made by calculating differences between the posterior distributions of the response rate between each dose of GSK3640254+DTG arm to the control arm DTG/3TC, which will be summarized to obtain posterior means and CIs. The point estimates of differences in virologic response rate with 95% credible intervals will be calculated for the treatment comparisons.

Posterior probability for the differences of following comparisons will also be reported.

1. Response rate GSK3640254 100 mg + DTG vs. Response Rate Control arm DTG/3TC
2. Response rate GSK3640254 150 mg + DTG vs. Response Rate Control arm DTG/3TC
3. Response rate GSK3640254 200 mg + DTG vs. Response Rate Control arm DTG/3TC

Besides, frequentist treatment difference point estimate and associated 95% confidence intervals will also be displayed.

9.1.3. Population of Interest

The primary efficacy analyses will be based on the Intent-to-Treat Exposed (ITT-E) and Per Protocol Population for sensitivity analysis.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events such as discontinuations, missing plasma HIV-1 RNA samples and change in background regimen are handled using the Snapshot algorithm (see Appendix 15.4.4), which details how to assign each participant's virologic outcome.

9.1.5. Statistical Analysis/Method

9.1.5.1. Primary Endpoint Statistical Methodology Specification

Endpoint / Variables
• Binary outcome indicating the virologic category of plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 24 using the FDA Snapshot algorithm
Model Specification
• Posterior distributions of the response rates for each dose, d, of GSK3640254+DTG and the reference DTG/3TC treatment will be calculated according to the following Bayesian model and parameters: • $p_d = probability\ of\ response\ on\ dose\ d$ $$p_d = \frac{e^{\theta_d}}{1 + e^{\theta_d}}$$ • $\theta_d = Log\ odds\ of\ probability\ of\ response\ for\ dose\ d$ $$\theta_d = \ln\left(\frac{p_d}{1 - p_d}\right)$$ **Model details:** A Bayesian hierarchical model will be fitted using MCMC methods (Jones HE, 2011), the noninformative prior Beta (1,1) will be utilized for the reference arm to estimate the posterior probability of virologic response rate (Week 24 response rate, defined as the proportion of participants with plasma HIV-1 RNA < 50 c/mL as calculated by the FDA snapshot algorithm for GSK3640254+DTG dose arms and reference arm DTG/3TC incorporating the baseline analysis stratification factors defined below.

Baseline Analysis Strata

Stratum	B_1: Baseline HIV-1 RNA ($I_{\{B1+\}}$)
<100,000 copies/mL	B_1-(<100,000 c/mL) (0)
≥100,000 copies/mL	B_{1+}(≥100,000 c/mL) (1)

Model for each arm:

$$Number\ of\ responders\ r_g \sim Binomial(n_g, p_g), \qquad g = 1,2$$

$$\theta_g = logit(P_g) = \log\left(\frac{P_g}{1-P_g}\right) = \gamma_0 + \gamma_1 I_{\{B1+\}} + \psi_g, \qquad g = 1,2$$

Where $\gamma_0, \gamma_1, \psi_g$ are all parameters. Thus,

$\theta_1 = \gamma_0 + \psi_1$

$\theta_2 = \gamma_0 + \gamma_1 + \psi_2$

Priors:

$\gamma_k \sim Normal(0, 10^6), k = 0,1$

$\psi_g \sim Normal(0, \omega^2), g = 1,2$

$\omega \sim Half - normal(1)$

Where we define r_g as the number of Virologic responders among n_g participants, p_g as Virologic response rate $\frac{r_g}{n_g}$, θ_g as the log odds of treatment response $\log(\frac{p_g}{1-p_g})$, index g =1,2 refers to the analysis stratum number, γ_k represent fixed effects of baseline analysis stratification factors (see below), and ψ_g denotes a random effect in analysis stratum g.

The two analysis strata and representation of the one baseline analysis stratification factor B_1 in the model are shown in Table above.

For each arm, the posterior distribution of Virologic response rate $P(p_g|data)$, g=1,2 will be derived for each analysis stratum using the model specified above.

$$P(p_1|data) = P(\frac{e^{\theta_1}}{1+e^{\theta_1}}|data)$$

$$P(p_2|data) = P(\frac{e^{\theta_2}}{1+e^{\theta_2}}|data)$$

The posterior distribution of the arm-level Virologic response rate will be derived using a mixture of the posterior distributions of Virologic response rate for each analysis stratum in that arm. The weights are proportional to the sample size of each analysis stratum in each arm.

$P(p\|data) = \sum_{g=1}^{2} w_g P(p_g\|data)$, where $w_g = \frac{n_g}{\sum_{g=1}^{2} n_g}$
Model Checking & Diagnostics
• Specific model checking procedures will be implemented according to the "Bayesian Statistics Best Practice at GSK- Clinical Trials Using Bayesian Inference document.
Model Results Presentation
• A figure will be produced which displays the posterior distribution of response rate for each of the doses of GSK3640254+DTG as well as the posterior distribution of response rate for the DTG/3TC control arm. • The mean of the posterior distribution of Week 24 snapshot response rate as well as associated 95% highest posterior density credible interval will be calculated for each dose of GSK3640254+DTG and the reference DTG/3TC arm and presented in tabular form
Sensitivity and Supportive Analyses
• As a sensitivity analysis, to assess the impact of significant protocol deviations, statistical analysis will be repeated using the Per-Protocol population and compared for consistency with the results from the primary ITT-E population analysis. • As supportive analysis and to assess the robustness of the primary analysis, a strata-adjusted Cochran-Mantel-Haenszel (CMH) test would be conducted to estimate treatment risk difference on binary response indicating virologic outcome category of plasma HIV-1 RNA <50 copies/mL (c/mL) at 24 week, using the FDA Snapshot algorithm, adjusting for Baseline HIV-1 RNA (<100,000 copies/mL or ⩾100,000 copies/mL) between doses of (GSK3640254+DTG) and control group (DTG/3TC) and its corresponding 95% confidence interval will be presented. For the analysis details please see section 9.2.6.

Number and percent of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 24 observed as well as using the FDA Snapshot algorithm, will be also tabulated by treatment with Clopper Pearson 95% confidence intervals also presented graphically.

Efficacy listings will be generated.

9.2. Secondary Efficacy Analyses

9.2.1. Endpoint / Variables

Secondary analyses will be conducted on:

- Absolute values and changes from baseline in HIV-1 RNA through Weeks 24
- Absolute values and changes from baseline in CD4+ T-cell counts through Weeks 24

9.2.2. Summary Measure

Number and percent of participants with HIV-1 RNA <50 copies/mL (c/mL) for both observed and snapshot analysis (see Appendix 15.4.4) within each treatment group (GSK3640254+DTG) and Control group (DTG/3TC) at week 24 will be also tabulated by treatment and visit with Wilson 95% confidence intervals and presented graphically over time.

Study outcome category and reasons defined by snapshot algorithm will also be summarized by treatment at Week 12, Week 24.

Descriptive statistics (mean, median, standard deviation, etc.) of absolute values and changes from baseline in HIV-1 RNA, Log10 of HIV-1 RNA, CD4+ T-cell counts through weeks 24 and presented graphically over time on ITT-E population.

9.2.3. Population of Interest

The secondary efficacy analyses will be based on the Intent-to-Treat Exposed (ITT-E), unless otherwise specified.

9.2.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events such as discontinuations, missing plasma HIV-1 RNA samples and change in background regimen are handled using the Snapshot algorithm (see Appendix 15.4.4), which details how to assign each participant's virologic outcome.

9.2.5. Statistical Analyses / Methods

Unless otherwise specified, endpoints / variables defined in Section 9.2.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

There will not be any formal statistical analysis of secondary endpoints. Only descriptive statistics will be reported.

Details of the planned displays are provided TLFs Shells document.

9.2.6. Statistical Methodology Specification

Endpoint / Variables
The binary response indicating the virologic outcome category of plasma HIV-1 RNA <50 copies/mL (c/mL) at weeks 24 using the FDA Snapshot algorithm (see Appendix 15.4.4)
Model Specification
The efficacy endpoint will be analysed using a stratified analysis for proportions with Cochran-Mantel-Haenszel (CMH) weights, adjusting for Baseline HIV-1 RNA (<100,000 copies/mL or ≥100,000 copies/mL). Details of the analysis strata can be found in the Section 7.6.1. 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 2 analysis strata: • <100,000 copies/mL • ≥100,000 copies/mL If n_k is the number of Treatment treated participants, m_k is the number of Comparator treated participants, and $N_k = n_k + m_k$ is the total number of participants in the kth stratum, then the CMH estimate is given by $$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

where,

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

are CMH weights and d_k are estimates of the differences in proportions of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) between the two treatment arms (Doses of GSK3640254 +DTG), $r_{GSK3640254\ +DTG} - r_{DTG/3TC}$, for the kth strata.

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

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

where the variance estimator (Sato, 1989) is consistent in both sparse data and large strata and is given below

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

where

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

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

with x_k and y_k corresponding to the number of participants with HIV-1 RNA <50 copies/mL (c/mL) at weeks 24 as determined by the FDA Snapshot algorithm (see Appendix 15.4.4), for treatment and comparator, respectively, for the kth stratum.

Model Checking & Diagnostics

- Not applicable, as no formal statistical modeling is being performed

Model Results Presentation

Adjusted CMH estimate of the difference in the percent of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) between each treatment group (GSK3640254+DTG – DTG/3TC) and corresponding 95% confidence interval will be presented.

Subgroup Analyses

- An analysis for subgroups listed in Section 7.6.2 will be performed. This will show the percent of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) at the time of analysis (Weeks 24) based on the Snapshot algorithm and will be presented by treatment group. Unadjusted percent by subgroup and corresponding two-sided 9 (FLEISS, 1981)5% (Wilson Score) confidence intervals will be tabulated and may also be presented graphically in a forest plot.

Sensitivity and Supportive Analyses

- Separate supportive analyses will be performed to enable the assessment of the homogeneity of the treatment difference across analysis strata used in the analysis.

  The weighted least squares chi-squared statistic of (FLEISS, 1981) will be used to test for one-way homogeneity of the treatment difference across the levels of the strata used for the primary analysis. The overall test for homogeneity will use the combined strata levels constructed by cross-classification of Baseline HIV-1 RNA . Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any stratum for which the stratum-specific estimates of either $r_{GSK3640254+DTG}$ or $r_{DTG/3TC}$ are zero or one, and tests will be one-sided. Tests of homogeneity will be assessed at the one-sided 10%

level of significance.

For each stratum, the percent of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) by treatment group and unadjusted difference in percent between treatment groups with corresponding two-sided 95% CI (using the Wilson Score method) will be reported. In addition, the p-value from the overall test of homogeneity will be reported. These results will be used to assess the statistical assumption underlying the CMH stratified analysis procedure - namely the assumption on a common treatment difference across strata.

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10. Pharmacokinetics

10.1. Endpoint / Variables

Only pharmacokinetic concentration will be part of this SAP. All participants will provide samples for Sparse PK at Weeks 2, 4, 8, 12, 24 as outlined in the SoA. Please refer Table 1.

10.1.1. Drug Concentration Measures

All PK concentration listing displays will be based on the Sparse Pharmacokinetic populations and will be sorted by subject, study visit and time (or sampling window) relative to dose.

The plasma concentration levels of the drug will be summarized descriptively by treatment group, visit and timepoint for week 2, 4, 8, 12, 24.

10.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters are out of scope of this analysis plan since intensive PK was not collected in this study. Further details on PK parameter analysis for GSK3640254+DTG will be included in a separate SAP.

11. Virology

The virology analyses of genotype and phenotype data will be based on the Viral Genotypic, Phenotypic and PDVF populations with subjects having Viral load >= 200 c/ml.

The PDVF population will be based on subjects who have experienced a PDVF at any point.

Refer to protocol section 7.1.1 and SAP Section 15.4.5 for the details of the PDVF details.

Summary tables will present PDVFs up to and including the time point of interest . PDVFs must be confirmed within the phase in which they are reported.

Listings will present PDVFs occurring at any point.

Full sequence reverse transcriptase (RT), integrase inhibitors (INI), protease inhibitors (PI), and the study drug GSK3640524+DTG maturation inhibitors (MI) available data will be analysed at baseline, Week 4, and at time of confirmed protocol-defined virologic failure for baseline mutations and for emergent mutations. Additionally, genotypic changes from baseline will be identified and listed to potentially identify pathways to resistance. These analyses will use the PDVF population.

Phenotypic changes for approved drugs will be determined at baseline, Week 4, and at time of confirmed PDVF. Treatment Emergent phenotypic changes will be investigated in the on-treatment Genotypic and Phenotypic population.

Please refer SAP shells for further details on displays related to virology.

12. Safety

Safety analyses will be conducted using the Safety Population unless otherwise specified..

Safety will be assessed based on extent of exposure, adverse event (AE) reports, relevant COVID-19 Assessments, AESI, vital signs, CCI clinical laboratory data, C-SSRS using descriptive statistics.

No inferential statistical analyses are planned on the safety parameters of this study.

12.1. Extent of Exposure

Extent of exposure including Time on Study Treatment (days), Subject Daily Dose (mg), and Cumulative Actual Dose (mg) will be summarized by treatment group using descriptive statistics for Week 24 on safety population. The subject daily dose (the cumulative actual dose divided by the duration of exposure in days) is calculated for each subject first and the summary statistics are calculated based on the subject average daily dose.

A listing presenting all above defined variables of extent of exposure and study drug administration data including dates for administration, dispensing and dose interruption details will be presented for the safety population.

12.2. Adverse Events

Unless otherwise stated AE mentioned in this section refers to Treatment-Emergent AEs.

Any AE will be considered a treatment-emergent adverse event (TEAE) if it occurred after the first dose of study intervention and within five days after treatment discontinuation. Where time of the AE start is not available, the AE will be considered a TEAE if it occurred on the same day as first dose of study intervention. For AE happened in subjects with more than one treatment, AE is assigned to the most recent treatment to the AE start date.

Flag	Definition
Treatment Emergent	• Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 5 days. • For AE happened in subjects with more than one treatment, AE is assigned to the most recent treatment to the AE start date.

NOTES:
- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

Adverse events will be summarized by system organ class (SOC) and preferred term (PT) for each treatment and total, based on the MedDRA dictionary version 25.0 or above. Severity of AEs will be graded according to The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1), July 2017. A grading (severity) scale is provided for each AE term.

Table for Grading the Severity of Adult and Pediatric Adverse Events.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING

Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Duration will be calculated for AEs that resolve as the difference between the resolution date and onset date plus 5 and expressed in days.

The summary tables will include the number of patients and the number of events. Percentages will be based on the number of patients in the safety population. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level.

For summaries by SOC, PT, and maximum severity, a patient will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by total descending frequency of SOC and then, within a SOC by total descending frequency of PT.

The following summaries of AEs will be provided:

- AEs by system organ class and preferred term
- AEs with maximum DAIDS toxicity grade by system organ class and preferred term
- Drug-related AEs with maximum DAIDS toxicity grade by system organ class and preferred term;
- All Grade 2-5 Adverse Events by System Organ Class, Preferred Term
- Non-Serious AE by system organ class and preferred term
- SAEs by system organ class and preferred term;
- SAEs with maximum DAIDS toxicity grade by system organ class and preferred term
- Drug-related SAEs by system organ class and preferred term
- AEs leading to Withdrawal/Permanent Discontinuation of Study Intervention/ Withdrawal from Study by system organ class and preferred term;
- AEs leading to death by system organ class and preferred term;
- AEs of special interest by system organ class and preferred term;

AE Listings will include complete list of subjects having AEs in the safety population (irrespective of treatment emergent). Additional listings will be provided for AESIs, serious AEs and Adverse Events Leading to Study Drug Discontinuation/Withdrawal from Study.

12.3. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event in a separate document (AESI MedDRA). Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from ongoing studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of

interest and the specific events of interest are defined at a compound level and based on the safety review team (SRT) agreements in place at the time of reporting.

Current AESI categories are as follows:

- QT prolongation
- GI intolerability/toxicity

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- Nervous System Disorders
- Skin and subcutaneous tissue disorders
- Cardiac Disorders

Adverse events of special interest categories will be summarized separately using descriptive statistics and will not undergo formal statistical analysis.

12.4. COVID-19 Assessments

Relevant COVID-19 Assessments, COVID-19 Symptoms for Subjects with Adverse Events, and COVID-19 Pandemic Visit Impacts will be summarized.

12.5. Laboratory Data

Safety laboratory samples for chemistry, hematology and urinalysis will be collected at various visits. Refer to Section 5.6 for the schedule of activities indicating when the respective samples are taken.

All parameters are listed in Table 13 of Section 10.2 of the protocol.

The following descriptive summaries for data will be provided:

N (number of subjects in the population), n (number of subjects used for the analysis), arithmetic mean, 95% CI for the arithmetic mean, SD, median, minimum, maximum for the untransformed data.

Actual values and changes from baseline in chemistry and hematology will be summarized by visit using descriptive statistics. Maximum treatment emergent hematology and clinical chemistry toxicities (DAIDS grading) will also be presented as summary table.

Lipids

Statistical Analyses
Endpoints
• Change from Baseline in Fasting Lipids (Triglycerides, LDL cholesterol, HDL cholesterol, Total Cholesterol and TC/HDL ratio) at Weeks 24
Analysis Specification
• The data will not be log transformed for the lipids and will be presented on the normal scale.
Results Presentation

Statistical Analyses
• N (number of subjects in the population), n (number of subjects used for the analysis), arithmetic mean, 95% CI for the arithmetic mean, SD, median, minimum, maximum will be presented for the untransformed data.

All laboratory results will be included in data listings.

12.6. Other Safety Data

The analyses of non-laboratory safety test results including CCI vital signs, liver events, Columbia Suicide Severity Rating Scale (C-SSRS).

12.6.1. Liver events

A summary of subjects meeting hepatobiliary laboratory abnormality criteria at any post-Baseline emergent visit will also be produced based on FDA Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009). In addition, a summary and listing of subjects with Liver Stopping Events will also be produced.

12.6.2. Columbia Suicide Severity Rating Scale

As per protocol eC-SSRS should be summarized by visit, as this is not applicable to this study, a summary table presenting number of patients with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be generated only by treatment. Patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent based on the eC-SSRS will also be listed.

CCI

CCI

12.6.4. Vital Signs

Vital signs will include average systolic blood pressure (mmHg), average diastolic blood pressure (mmHg), average heart rate (beats per minute, bpm), respiration rate (breaths per minute), and body temperature (°C). Summary tables of the actual values and changes from baseline will be provided for each vital sign parameter at each scheduled visit by treatment group and in total.

Additionally, body weight and BMI will be summarized with actual values and change from baseline at each scheduled visit by treatment group, and in total.

Vital signs data will be listed for safety set patients.

Vital Sign Parameter (Absolute)	Units	Potential Clinically Important Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>140
Diastolic Blood Pressure	mmHg	<45	>90
Heart Rate	bpm	<40	>100

13. Changes from Analysis Planned in Protocol

This section details the changes from analysis planned in protocol.

As the study has been terminated before Week 48, any planned protocol-defined analysis related to Week 48/52 will not be performed, instead an end of study analysis will be conducted based on the available data from Day 1 to EoS.

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907.02).

Syneos Health Developing Statistical Programs SOP (3907.02), Conducting the Transfer of Biostatistical Deliverables SOP (3908.03) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. Appendix:

15.1. Appendix 1: Exclusions from Per Protocol Population

A participant meeting any of the following criteria will be excluded from the Per-Protocol population:

Number	Exclusion Description
01	Subject deviates from any inclusion or exclusion criteria, as recorded in the eCRF
02	Subject took/received incorrect study treatment (GSK3640254+DTG or DTG/3TC), i.e., other than the one to which they were randomized for more than 10% of the total time On-treatment
03	Interruption/dose modification of randomized regimen (GSK3640254+DTG or DTG/3TC) for longer than 10% of the total time on-treatment for reasons other than treatment related adverse events/laboratory abnormalities. Derivation will be based on concomitant medication and IP eCRF forms.
04	Prohibited medications: receiving ART medication other than that prescribed/allowed by the study for more than 7 days or receiving prohibited Concomitant medication that would impact exposure or response to therapy with duration taken into consideration. The following, general concomitant medications or therapies are not permitted at any time during the study: HIV immunotherapeutic vaccines are not permitted at any time during the study. Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered. Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SRM) This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted. Acetaminophen (paracetamol) cannot be used in patients with acute viral hepatitis. Note: For treatment specific prohibited meds refer in Section 6.8.1.3. and 6.8.1.4. of the protocol
05	Permanent discontinuation of IP/withdrawal due to a reason of "Protocol Deviation" (as recorded in the eCRF).

15.2. Appendix 2: Assessment Windows

1. Definitions of Assessment Windows for Snapshot Analyses

Analysis Set / Domain	Parameter (if applicable)	Target (Day)	Analysis Window (Day)		Analysis Timepoint	Window Weeks
			Beginning Timepoint	Ending Timepoint		
Efficacy	Snapshot Endpoint	-63		<-3	Screen	NA
		1	-3	1	Day 1	NA
		15	2	21	Week 2	Day 2 ~ Week 3
		29	22	42	Week 4	3~6
		57	43	70	Week 8	6~10
		85	71	98	Week 12	10~14
		113	99	126	Week 16	14~18
		169	**127**	**210**	**Week 24**	**18-30**

NOTES:

1. The Snapshot visit windows are used as part of the Snapshot algorithm to determine a participant's category.
2. Week 24 follow FDA Snapshot Algorithm to use +/- 6 weeks as the analysis window. Apply Snapshot analysis windows only to viral load data that is on-treatment
3. Other analyses visits will use analysis windows ½ the distance between the previous and subsequent timepoint.
4. Snapshot analysis is performed only upto Week 24

2. Definitions of Assessment Windows for Other Analyses

Other analyses Sets (e.g. lab) will use analysis windows ½ the distance between the previous and subsequent timepoint.

Analysis Set / Domain	Parameter (if applicable)	Target (Day)	Analysis Window (Day)		Analysis Timepoint	Window Weeks
			Beginning Timepoint	Ending Timepoint		
Efficacy (Observed)/Safety (Lab, CCI VS)/Virology[1]	All	-63		<-3	Screen	NA
		1	-3	1	Day 1	NA
		15	2	21	Week 2	Day 2 ~ Week 3
		29	22	42	Week 4	3~6
		X*7+1	(X-2)*7+1	(X+2)*7	Week X, X=8, 12, … , 52, once every 4 weeks from Week 8 to 52	(X-2) ~(X+2)

Analysis Set / Domain	Parameter (if applicable)	Target (Day)	Analysis Window (Day)		Analysis Timepoint	Window Weeks
			Beginning Timepoint	Ending Timepoint		
		X*7+1	(X-2)*7+1	(X+4)*7	Week X, X= 56	(X-2) ~(X+4)
		X*7+1	(X-4)*7+1	(X+4)*7	Week X, X= 64, 72, 80,88	(X-4) ~(X+4)
		Study Day of last dose + 28	> =(Study Day of last dose + 28)		Follow-up	NA
Safety	CSSRS	-63		<-3	Screen	NA
		1	-3	1	Day 1	NA
		15	2	21	Week 2	Day 2 ~ Week 3
		X*7+1	(X-2)*7+1	(X+2)*7	Week X, X>=4, In Clinic and Virtual Visit	(X-2) ~(X+2)
		Study Day of last dose + 28	> =(Study Day of last dose + 28)		Follow-up	NA

NOTES:
1. For safety endpoints and some other results collected for virtual visits, please refer to protocol section 1.3 SOA for details.

15.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

Study Phases
Assessments and events will be classified according to the time of occurrence relative to Insert Study Specific Text Here

Study Phase Overall Data

Study Period	Definition
Randomized Phase	If the subject does not switch to 100 mg: Study Treatment Start Date < Date ≤ End of Study Date + 5 days If the subject does switch to 100 mg: Study Treatment Start Date < Date ≤ Optimal Dose Switch Start Date
Switch Phase	Optimal Dose Switch Start Date < Date ≤ Optimal Dose Switch End Date + 5 days.

Study Phase for Laboratory, HIV Associated Conditions, Genotypic and Phenotypic Data

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 5 days
Post-Treatment	Date > Study Treatment Stop Date + 5 days

Datetime will be used. If time part is not available, date would be used instead.

Study Phase for Adverse Events and Exposure

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date <= Date ≤ Study Treatment Stop Date + 5 days
Post-Treatment	Date > Study Treatment Stop Date + 5 days

Datetime will be used. If time part is not available, date would be used instead.

Study Phases for Concomitant Medication

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

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

NOTES:

Please refer to Appendix 5: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 5 days. • For AE happened in subjects with more than one treatment, AE is assigned to the most recent treatment to the AE start date.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

15.4. Appendix 4: Derived and Transformed Data

15.4.1. General

Multiple Measurements at One Analysis Time Point
• If there are multiple assessments within Screening window, the last assessment before Day 1 will be used • If there are multiple assessments within Day 1 window, the latest pre-dose assessment will be used • With the exception of the Snapshot endpoints, if after window assignment, there are multiple valid assessments of a parameter within the same window, then the following hierarchy will be used to determine the value to be used for summary statistics of observed values: • the assessment closest to the window target Study Day; • if there are multiple assessments equidistant from the target Study Day, then for continuous variables the mean of these values will be used and for categorical variables the worse assessment. For HIV-1 RNA, the geometric mean of the number of copies will be used as opposed to the arithmetic mean • Assessments not chosen for use in summary statistics by this algorithm will still appear in the associated listings. Also, such valid assessments will be used when determining values of potential clinical concern for the 'any time On-treatment' time point, and for any algorithm that has specific rules for which observation to use (e.g., SNAPSHOT). •
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

15.4.2. Study Population

Extent of Exposure
• Number of days of on treatment will be calculated based on the formula: **Duration of Treatment in Days = Treatment Stop Date – (Treatment Start Date) + 1** This information will also be categorized as: < 12 weeks, 12 to 24 weeks, >24 weeks to 48 weeks, > 48 weeks to 108 weeks, > 108 weeks • Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Sum of Number of Days on Dose** This information will also be categorized as: < 12 weeks, 12 to 24 weeks, >24 weeks to 48 weeks, > 48 weeks to 108 weeks, > 108 weeks • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • "Dose interruption/delay days contribute to calculation of total dose exposure".
Demographics
Age
• GSK Statistical Display Standard algorithms will be used for calculating age where birth date will be imputed as follows: ○ For all subjects, the 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.

15.4.3. Efficacy

HIV-1 RNA

Snapshot

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

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

- Full details of the algorithm, including the handling of special cases, are included in Section 15.4.4 of note, the date at which the subject 'discontinue/withdrawn from the study' in the Snapshot algorithm is the date of treatment discontinuation, rather than the date of study withdrawal,

Plasma HIV-1 RNA

- For summaries and analyses which use HIV-1 RNA level as a continuous measure, the logarithm to base 10 of the value will be used.
- HIV-1 RNA results may be provided as censored values, such as <40 or >9,999,999 c/mL. For the purposes of summary statistics, such values will be replaced by the next value beyond the limit of detection, e.g., 39 or 10,000,000 c/mL, respectively, for the given examples. Data listings will show the censored values as provided.
- Qualitive measures (i.e. "target detected" and "target non-detected") may also be provided by the laboratory vendor for values <40 c/ml. When a measurement of plasma HIV-1 RNA is below the limit of quantification (i.e. 40 c/mL) and is qualitatively observable that will be denoted as a "Target Detected" measure, while HIV-1 RNA below the limit of quantification that is not qualitatively observable that will be denoted as "Target Not Detected". Any measurements <40 c/mL characterized as "Target Non-Detected" or "Target Detected" will be captured in the database.

CDC HIV-1 Classification and HIV-associated conditions

- HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see protocol Section 10.10).
- Any 'other' conditions reported in the eCRFs will be identified programmatically before being sent for clinical review to determine whether they should be classed as stage 3 associated conditions. Review will be ongoing and as a minimum will take place prior to each reporting effort.

15.4.4. Snapshot Algorithm Details

- Consider an analysis visit window, Week X (e.g., Week4, …Week 24, ..Week 48 etc.). The Window for Week X visit is defined in Appendix 15.2. e.g. Week 48 (+/- 2 Week: 323 ≤ Study Day ≤ 350)

- Consider an HIV1-RNA threshold (e.g. 40, 50, 200 copies/mL …) for a given analysis. Our study will use 50 copies/mL as threshold.
- For example: The analysis window 'Week 48' and HIV1-RNA threshold of '50 copies/mL' are used for the purposes of illustration. A participant's Snapshot response and reason at Week 48 are categorized as below.

  - o HIV1-RNA < 50 copies/mL
  - o HIV1-RNA >= 50 copies/mL

    Data in window not below 50

    Discontinued for lack of efficacy

    Discontinued for other reason while not below 50

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

    Discontinued study due to AE or death

    Discontinued study for other reasons

    On study but missing data in window

*All changes are considered non-permitted.

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

Detailed steps
Please note that the following scenarios will NOT be penalized Per Snapshot algorithm (i.e. please exclude these scenarios from **Condition** 1-4). • Dose reduction, dropping a component, or change in formulation (e.g. 'Tivicay + Kivexa' to 'Triumeq' with the identical ingredients) • Permitted Change in ART where date of change or date of decision to make permitted change (whichever is earlier) occurs prior to/on the first on-treatment viral load result

Condition (Note that: "Week XX" indicates Week XX window. Week 48 is used as an example below)	**Response**	**Reasons**
1. If ***non-permitted*** change in background therapy ***prior to*** Week 48	HIV1-RNA ≥ 50	Change in background therapy
2. If ***permitted*** change in background therapy ***prior to*** Week 48 AND the latest on-treatment VL prior to/on the date of change is ≥ 50 c/mL [a]	HIV1-RNA ≥ 50	Change in background therapy
3. If ***non-permitted*** change in background therapy ***during*** Week 48		

• 3.1 Last on-treatment VL during Week 48 prior to/on the date of change ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window not below 50
• 3.2 Last on-treatment VL during Week 48 prior to/on the date of change <50 c/mL	HIV1-RNA < 50	
• 3.3 No VL during Week 48 prior to/on the date of change	HIV1-RNA ≥ 50	Change in background therapy
4. If ***permitted*** change in background therapy ***during*** Week 48 AND the last on-treatment VL prior to/on the date of change is ≥ 50 c/mL [a]		
4.1 this last on-treatment VL occurs prior to Week 48	HIV1-RNA ≥ 50	Change in background therapy
4. 2 this last on-treatment VL occurs during Week 48 but prior to/on the date of change	HIV1-RNA ≥ 50	Data in window not below 50
5. If none of the above conditions met		
5.1 VL available during Week 48		
5.1.1 Last on-treatment VL during Week 48 ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window not below 50
5.1.2 Last on-treatment VL during Week 48 <50 c/mL	HIV1-RNA < 50	
5.2 No VL during Week 48		
5.2.1 If participants still on study (i.e. The on-treatment period continues beyond the upper bound of Week 48 window. For example, for oral treatment, a participant with IP stop date+1> Day 378 of the upper bound of Week 48 window, would be considered 'on study' for Week 48 snapshot assessment)	No virologic data at Week 48 Window	On study but missing data in window
5.2.2 If participants withdraw before/during Week 48 due to :		
5.2.2.1 Safety reasons (e.g. AE/death, liver chemistry stopping criteria, renal toxicity withdrawal criteria, QTc withdrawal criteria, as recorded in eCRF Conclusion form)	No virologic data at Week 48 Window	Disc. due to AE/death
5.2.2.2 Non-safety related reasons (e.g. Lack of efficacy, protocol deviation, withdrew consent, loss to follow-up, study closed/terminated, investigator discretion et al, as recorded in eCRF Conclusion Form)		
5.2.2.2.1 Last on-treatment VL <50 c/mL OR no on-treatment VL available during study	No virologic Data at Week 48 Window	Disc. for other reasons
5.2.2.2.2 Last on-treatment VL ≥ 50 c/mL AND withdrawal due to Lack of efficacy	HIV1-RNA ≥ 50	Disc. for lack of efficacy
5.2.2.2.3 Last on-treatment VL ≥ 50 c/mL AND withdrawal due to all other non-safety related reasons	HIV1-RNA ≥ 50	Disc. for other reason while not below 50

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

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

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

15.4.5. Virology

PDVF

PDVF is defined as any of the following (and confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between two and four weeks (approx.) after the initial suspected virologic failure sample):

Virologic Non-response

1. Decrease from Baseline (Day 1) in plasma HIV-1 RNA of <1.0 log10 c/mL unless plasma HIV-1 RNA is <200 c/mL by Week 12;
   - **SVF**: If there is a decrease < 1 log10 from Baseline at Week 12 and HIV-1 RNA >=200 c/mL, then -> Suspected Virologic Failure
   - **PDVF:** If there is a confirmatory sample after 1a, then check if there is a decrease <1 log10 from Baseline and the HIV-1 RNA >=200 c/mL then -> Protocol Defined Virologic Failure

2. Confirmed plasma HIV-1 RNA levels ≥200 c/mL at or after Week 24.
   - **SVF:** If a patient has a sample on/after Week 24 and the result is >=200 c/mL then -> Suspected Virologic Failure
   - **PDVF:** If after 2c, a patient then has a 2nd consecutive sample >=200 c/mL on/after Week 24 then -> Protocol Defined Virologic Failure.
3. Plasma HIV-1 RNA ≥50 c/mL on repeat testing of Week 24 results and prior to Week 28.
   - **SVF**: If a patient has a sample at Week 24 and the result is >=50 c/mL then -> Suspected Virologic Failure
   - **PDVF**: If after 3e, a patient then has repeat (retest) sample prior to Week 28 then -> Protocol Defined Virologic Failure.
4. **Virologic Non-response: If a subject met criteria 1b or 2d or 3f then -> PDVF (Virologic Non-response)**

Virologic Rebound

5. Confirmed plasma HIV-1 RNA ≥200 c/mL after confirmed consecutive plasma HIV-1 RNA <50 c/mL.
    - Patient must have 2 consecutive values <50 c/mL, followed at any time (not necessarily immediately) by 2 consecutive values >=200 c/mL
    - **SVF**: If a patient has two consecutive samples <50 c/mL, if any following value is >=200 c/mL then -> Suspected Virologic Failure
    - **PDVF**: If after 5g, a patient then has a 2nd consecutive sample >=200 c/mL then -> Protocol Defined Virologic Failure.
6. Virologic Rebound: If a subject met criteria 5h then -> PDVF (Virologic Rebound)

7. Current plasma HIV-1 RNA levels ≥200 c/mL after Week 24

    a. SVF: If a patient has a sample after Week 24 and the result is >=200 c/mL when previous results was <50c/mL then -> Suspected Virologic Failure

    b. PDVF: If a patient has a sample after Week 24 and the result is >=200 c/mL when previous results was >=50c/mL then -> PDVF (Virologic Non-Response)

Genotype

General considerations

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

Amino Acid Changes

- A mutation is considered present whenever the encoded amino acid residue differs from the amino acid that would have been encoded by the wild-type (e.g., HXB2, NL43) comparator gene; e.g., Q148K.
- If the encoded amino acid is seen as a mixture of wild-type and mutant amino acid, e.g., Q148Q/K, the mutated amino acid is considered present at the codon of interest.
- If the encoded amino acid is seen as a mixture of two or more amino acids, which may or may not include wild type, e.g., Q184K/H or Q184K/H/Q, etc., for the purposes of calculating the number of mutated amino acids, only one mutation is considered to be present at the codon of interest.
- Treatment emergent mutations: need to meet below three criteria:
    1. New mutation: observed during treatment comparing to baseline at the same codon with the class/region.
    2. Mutations are based on prespecified lists usually identified in the SAP.
        a. Integrase: may use a list generated by Virology that may include non-IAS guidance mutations derived using the Stanford database (e.g., mutations with penalty score >=15; https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/), or other reliable sources. Note the list may change over time. Usually the major mutations are the ones with evidence of strong resistance to the ART drug.
        b. All other classes: defined by the International Antiviral Society-USA (IAS-USA).

3. ART Drug class related: based on the class of the ART the subjects are taking during the treatment and the new major mutation within that class will be considered.

Representation of Amino Acid Changes

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

Prespecified Lists – Resistance Associated Mutations

- Summaries and listings of resistance associated mutations in the Integrase Strand Transfer Inhibitor (INSTI) class will use the following pre-defined INSTI list of mutations associated with the development of resistance to BIC, RAL, EVG or DTG.

Category	Mutations
Pre-defined INSTI mutations	H51Y, **T66A/I/K**, L74M, **E92Q/V**/G, Q95K, T97A, G118R, **F121Y**, E138A/K, G140A/C/S, **Y143C/H/R/K/S/G/A**, **P145S**, **Q146P**, **S147G**, **Q148**N/**H/K/R**, **V151**I/**L**/A, S153F/Y, **N155H**/S/T, E157Q, G163R/K, S230R, R263K, L68V/I*, L74I*, E138T*, G193E*

NOTES:

- Current list includes INSTI mutations identified via the Stanford HIV Resistance database, or identified during in vitro passage of DTG, or as seen in previous DTG studies in INSTI-experienced subjects (i.e. ING112574) and may be modified in case of additional substantive data availability.
- INSTI mutations in bold have the maximum score of 60 and are for any INSTI drug in the Stanford database v9.1 (https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/,last updated on 2022-06-02); the rest have a maximum score <60.

1. Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) as defined by the International Antiviral Society-USA (IAS-USA). The most up to date IAS-USA guidelines available at the time of DBF will be used in the analysis. Note that NRTIs A62V, V75I, F77L, and F116Y all need to be present together with Q151M to be resistant, so are not major mutations alone.

Class	Mutations
NRTIs	M41L, K65R/E/N, D67N, K70E/R, L74V, Y115F, M184V/I, L210W, T215Y/F, K219Q/E; [A62V, V75I, F77L, F116Y, Q151M]
NNRTIs	L100I, K101E/P, K103N/S, V106A/M, V108I, E138/A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C, M230I

Pis	D30N,V32I , M46I/L, I47A/V, G48V, I50V/L, I54M/L/V, Q58E, T74P, L76V,V82A/T/F/L/S, N83D, I84V, N88S, L90M

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

Phenotype

Fold change (FC) in IC50 (concentration of drug required to inhibit the sample virus to 50% of its maximum) relative to wild-type control virus is reported from the assays. i.e., FC of sample virus = IC50 of sample virus/IC50 of control virus.
Summary statistics for FC will be reported at Baseline and at the PDVF timepoint (time of suspected failure, that was subsequently confirmed) for subjects meeting PDVF criteria.
Fold change ratio (Fold change at the time of PDVF/baseline Fold change) will also be summarised.

15.4.6. Safety

Adverse Events

AE Severity – DAIDS Grading

- The DAIDS grading (VERSION 2.1, March 2017) for severity of clinical adverse events will be performed.
- See protocol for DAIDS grading criteria.

Adverse Events of Special Interest (AESI)

The preferred terms for each AESI will be reviewed by safety and clinical team and updated before each formal analysis in a separate document. The following table below shows the AESI categories.

AESI

- QT prolongation
- GI intolerability/toxicity

CCI [redacted]

- Nervous System Disorders
- Skin and subcutaneous tissue disorders
- Cardiac disorders

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 smallest unit of one more significant digit than the number of significant digits in the observed values will be added or subtracted (whichever is applicable) in order to impute the corresponding number. For example:
  - Example 1: 2 significant digits (as in "<2.2") will be imputed as 2.19
  - Example 2: 1 significant digit (as in ">5") will be imputed as 5.1
  - Example 3: 0 significant digits (as in "<0") will be imputed as -1".
- There will be no imputation in the data listings; all values will be displayed as recorded in the database.

Lab Toxicities – DAIDS Grading

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

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

Glomerular Filtration Rate (GFR)

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

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

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

CKD-EPI Cystatin C Equation (2012)

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

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

Abbreviations / Units

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

Scys (standardized serum cystatin C) = mg/l

min = indicates the minimum of Scys/0.8 or 1

max = indicates the maximum of Scys/0.8 or 1

age = years

Assays

15.5. Appendix 5: Reporting Standards for Missing Data

15.5.1. 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 participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Snapshot	• In the Snapshot dataset, subjects without HIV-1 RNA data in the assessment window for the visit of interest (due to missing data or discontinuation of IP prior to the visit window) are classified as either 'HIV-1 RNA ≥50 c/mL') or 'No Virologic Data'. For full details of the Snapshot algorithm see Section 15.4.4
Observed Case (OC)	• This dataset uses only the data that is available at a particular timepoint, with no imputation for missing values.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

15.5.2. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • Where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases (see Section 15.3) or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Exposure	• If study treatment stop date is missing, then for the purposes of calculating exposure, it will be imputed using the date of last visit or the recorded date of withdrawal/completion whichever is earlier. • Partially Missing Stop Day: Last day of the month or last month of the year will be used, unless this is after the stop date of study treatment or withdrawal date; in this case the earliest of the two dates will be used.
Treatment End Date	• If subject is still on-going at data cut-off date, we assume the subject is still on-treatment, treatment end date will the last visit date.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • Partial dates for AE recorded in the CRF will be imputed using the following conventions: Missing start day: • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: ○ If month and year of start date = month and year of study treatment start date then

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>

▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.

○ Else set start date = 1st of month.
</td></tr>
<tr><td>Missing start day and month</td><td>
• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
○ Else set start date = January 1.
</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>

• Completely missing start or end dates will remain missing, with no imputation applied.
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>
• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.
</td></tr>
<tr><td>Missing start day and month</td><td>
• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>▪ Else set start date = study treatment start date.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
• The recorded partial date will be displayed in listings.
</td></tr>
</table>

15.6. Appendix 6: Time to Event Details

15.6.1. TRDF Detailed Steps

TRDF Detailed steps		
The steps below are for the derivation of TRDF at specific timepoints when the upper bound of the analysis window is used as a cut-off i.e. for the table only.		
Final step of the derivation is made in following order: [1] When one EVENT (1.2, 2.2, 3.2, 4.2) criterion is satisfied, select. In situations where more than one EVENT criteria satisfied, select the earliest event. If the earliest event date satisfies more than one criteria (e.g. subject had PDVF and discontinuation), select PDVF. [2] When one CENSOR (1.1, 2.1, 3.1, 4.1, 5.x) criterion is satisfied, select. Else in situations where more than one CENSOR criteria satisfied, select the latest censor day. If the latest event date satisfies more than one criteria, apply the ordering below.		
Condition	**Censor Status**	**Event Description/AVAL**
3. Subjects met PDVF event criteria during the randomized period. (Based on derived PDVF confirmed prior to cut-off used for the analysis) Then set **tempAVAL**= Study Day of PDVF		
1.1 PDVF event date is after the upper bound of the analysis visit window i.e tempAVAL > upper bound of the analysis visit window for Week X	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
1.2 PDVF event date is on or before the upper bound of the analysis visit window i.e tempAVAL ≤ upper bound of the analysis visit window for Week X	CNSR=0	EVNTDESC=PDVF. AVAL= tempAVAL.

4. Subjects with study withdrawal due to treatment related adverse events during the randomized period (defined as subjects that have reason for withdrawal =AE on disposition page and that the subject has at least one AE considered both: i) drug related (AEREL=Y) and ii) result in withdrawal from study (AEWD=Y)) Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Exposure and Concomitant ART domains]). Assumption: Study day of permanent treatment discontinuation is included in the definition to account for cases where discontinuation information is recorded later. This is a conservative approach consistent with treatment discontinuation preceding withdrawal.		
2.1 Study withdrawal is after the upper bound of the analysis visit window i.e tempAVAL > upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
2.2 Study withdrawal is on or before the upper bound of the analysis visit window i.e tempAVAL ≤ upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Treatment Related AE. AVAL= tempAVAL
3: Subjects met protocol defined stopping criteria during the randomized period., (Based on disposition page) Then set **tempAVAL**=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment		

discontinuation [from Study Treatment or CONART eCRF pages]).		
3.1 Protocol defined stopping criteria were met after the upper bound of the analysis visit window i.e tempAVAL > upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
3.2 Protocol defined stopping criteria were met on or before the upper bound of the analysis visit window i.e tempAVAL ≤ upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria. AVAL=tempAVAL
4: Subjects with study withdrawal due to lack of efficacy during the randomized period. (Based on disposition page) Then set **tempAVAL**= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study day of permanent treatment discontinuation [from Study Treatment or CONART eCRF pages])		
4.1 Study withdrawal is after the upper bound of the analysis visit window i.e tempAVAL > upper bound of the analysis visit window	CNSR=1	EVNTDESC=Censored due to data cutoff. AVAL=Upper bound of analysis visit window.
4.2 Study withdrawal is on or before the upper bound of the analysis visit window i.e tempAVAL ≤ upper bound of the analysis visit window	CNSR=0	EVNTDESC=Study Withdrawal Due to Lack of Efficacy AVAL= tempAVAL

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

7: Subject is ongoing in the study during the randomized period and have not yet completed the randomized period Assumption: this will only be in cases where the reporting effort/analysis is performed midway through the randomized period	CNSR=1	EVNTDESC= Censored due to data cutoff. AVAL=Upper bound of analysis visit window.

15.6.2. TRDF Detailed Steps for the Kaplan-Meier plot

TRDF Detailed steps		
The steps below are for the derivation of TRDF overall i.e. for the Kaplan-Meier plot only.		
Final step of the derivation is made in following order: [1] When one EVENT (conditions 1-4) criterion is satisfied, select. In situations where more than one EVENT criteria satisfied, select the earliest event. If the earliest event date satisfies more than one criteria (e.g. subject had PDVFand discontinuation), select PDVF. [2] When one CENSOR (conditions 5.x) criterion is satisfied, select. Else in situations where more than one CENSOR criteria satisfied, select the latest censor day. If the latest event date satisfies more than one criteria, apply the ordering below.		
Condition	**Censor Status**	**Event Description/AVAL**
5. Subjects met PDVF event criteria during the randomized period. (Based on derived PDVF confirmed prior to cut-off used for the analysis)	CNSR=0	EVNTDESC=PDVF. AVAL=Study Day of PDVF.
6. Subjects with study withdrawal due to treatment related adverse events during the randomized period (defined as subjects that have reason for withdrawal =AE on disposition page and that the subject has at least one AE considered both: i) drug related	CNSR=0	EVNTDESC=Study Withdrawal Due to Treatment Related AE. AVAL=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study Day of permanent treatment discontinuation [from Study Treatment eCRF pages]).

(AEREL=Y) and ii) result in withdrawal from study (AEWD=Y))		
3: Subjects met protocol defined stopping criteria during the randomized period., (Based on disposition page)	CNSR=0	EVNTDESC=Study Withdrawal Due to Protocol Defined Criteria. AVAL=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study Day of permanent treatment discontinuation [from Study Treatment eCRF pages]).
4: Subjects with study withdrawal due to lack of efficacy during the randomized period. (Based on disposition page)	CNSR=0	EVNTDESC=Study Withdrawal Due to Lack of Efficacy AVAL= Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study Day of permanent treatment discontinuation [from Study Treatment eCRF pages])
If none of the above conditions met		
5: Subjects with study withdrawal for other reasons on or before the end of randomized period. (Based on disposition page)	CNSR=1	EVNTDESC=Censored due to Study Discontinuation for Other Reasons. AVAL=Earliest of (Day of Study Discontinuation [from Disposition page]), date of Withdrawal Visit [from Study Visit domain], Study Day of permanent treatment discontinuation [from Study Treatment eCRF pages])
6: Subject completed the randomized period of the study. (Based on disposition page)	CNSR=1	EVNTDESC= Censored as completed the Randomized Period. AVAL= Date of completion of randomized study period
7: Subject is ongoing in the study during the randomized period and have not yet completed the randomized period	CNSR=1	EVNTDESC= Ongoing in the Study. AVAL=Last visit date

Notes:
Randomized Period = Randomized Phase

Efficacy visit windows should be used throughout for the upper bound of the analysis visit window
Subjects are considered to have completed the randomized period if they completed the Randomized Phase.
By definition, a subject must be on-treatment for a PDVF to be recorded therefore inclusion of study date of treatment discontinuation in the derivation is not required
EVNTDESC, AVAL & CNSR variables created for the following timepoints:
Week 24 – for the table analysis
Overall – for the Kaplan-Meier plot

15.6.3. ERDF Detailed Steps

Similar algorithm will be applied for ERDF analyses and Kaplan-Meier figure, where condition 2 and 3 in Section 15.6.1 and Section 15.6.2 will not be considered

15.6.4. Time to Viral Suppression

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

15.7. Appendix 7: End of Study Analysis

This appendix provides the details of the planned analyses and data displays for End of Study (EoS) reporting.

The primary analysis at Week 24 has been completed based on the original SAP. This present appendix is written to cover only analyses included in the end of study reporting.

The details of the EoS reporting and analysis plan are described below:

- The EoS analysis will include all the 4 treatment groups including data from Day 1 to EoS.
- Only specific outputs determined and described in the study analysis plan will be re-used for end of study reporting. Please refer to TLF Shells Section 2 for further details.
- No additional analysis is expected for EoS.

Overall Study (Data From Day-1 to EOS)

- 100 mg
- 150->100mg
- 200->100mg
- DTG/3TC

15.7.1. Study Phases

After the week 24 analysis, the subjects from 150 mg and 200 mg arm will be switched to the optimal dose of 100 mg. Whereas, subjects on DTG/3TC and 100 mg arm will remain on the same regimen until EoS.

For EoS reporting, data collected during randomized phase and switch phase in 150 and 200 mg arm and complete data till EoS in 100 mg and DTG/3TC arm will be considered.

15.7.2. Analysis Population for EoS

The study populations will remain the same as defined in Section 6 of the SAP.

15.7.3. Efficacy Analysis

For HIV-1 RNA viral load, all the summaries and listings defined in Section 9 of SAP will be used for EoS analysis except for the outputs using Snapshot algorithm. No formal inferential statistical analysis is planned.

Overview of the key planned efficacy endpoints:

- Proportion of Participants with Plasma HIV-1 RNA < 50 c/ mL/ >= 50 c/mL- observed data
- Proportion of Participants with Protocol-Defined Virologic Failure (PDVF) – observed data
- Incidence of disease progression and HIV-associated conditions
- Individual Plasma HIV-1 RNA and CD4+ Profiles

Full details of the data displays are given in Section 2 of the TLF shells document.

15.7.4. Safety Analysis

Only specific safety outputs at EoS will be included in EoS analysis. All safety displays will be based on the Safety population.

Overview of the key planned safety endpoints:

- Extent of Exposure
- Adverse Events/Special Interest
- Laboratory (Hematology, Chemistry)
- CCI [redacted]

Full details of the data displays are given in Section 2 of the TLF shells document.

15.7.5. COVID – 19 Analysis

The information regarding the number of participants affected by COVID-19 and its symptoms will be analyzed at EoS .

Full details of the data displays are given in Section 2 of the TLF shells document.

15.7.6. Virology Analysis

All the planned virology summaries and Listings with subjects who met Confirmed Virologic Withdrawal criteria will be part of EoS analysis.

All genotypic and phenotypic analysis at or prior to EoS will be included in the EoS analysis.

Full details of the data displays are given in Section 2 of the TLF shells document.

15.7.7. Pharmacokinetic analysis

Pharmacokinetic analysis would include all the data collected till the end of study with summaries and listing at EoS.

Full details of the data displays are given in Section 2 of the TLF shells document.

15.7.8. Other Analyses

Overview of the key other analyses:

- Liver Monitoring/Stopping Event Reporting
- Hepatobiliary Laboratory Abnormalities

Summaries and listings will be same at EoS.

Full details of the data displays are given in Section 2 of the TLF shells document.

16. References

FLEISS, J. (1981). *Statistical methods for rates and proportions. second edition.* New York: John Wiley & Sons.

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GSK_212483_DYNAMIC_RAP_Final_v2.0_17MAY2023_Clean

Final Audit Report 2023-05-19

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By:	PPD
Status:	Signed
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