TITLE PAGE

Protocol Title: A Phase III, randomized, multicenter, open-label, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir/lamivudine fixed dose combination in HIV-1 infected adults who are virologically suppressed

Protocol Number: 208090 Amendment 04

Compound Number: GSK1349572+GR109714 (GSK3515864)

Short Title: A Phase III, randomized, multicenter, open-label, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir/lamivudine fixed dose combination in HIV-1 infected adults who are virologically suppressed

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Approval Date: 05-MAY-2020

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In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Research and Medical Strategy

This study is sponsored by ViiV Healthcare. GlaxoSmithKline and PPD are supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): US IND: 127475/ EudraCT: 2018-000177-72

PPD

From: PPD
Sent: Wednesday, May 6, 2020 12:22 AM
To: PPD
Subject: FW: Prot-Amend4-208090-sponsign

Hello,

Please find sponsor approval below for 208090 amendment 04.

Kind regards,

PPD

From: Sherene Min PPD
Sent: Tuesday, May 05, 2020 1:38 PM
To: PPD
Subject: RE: Prot-Amend4-208090-sponsign

Dear PPD ,

I approve the protocol amendment.

Kind regards,

Sherene

Sherene Shakib Min, MD, MPH
VP, Head of Clinical Development

ViiV Healthcare
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PPD
M: PPD

PPD

From: PPD

Sent: Monday, May 04, 2020 1:31 PM
To: Sherene Min PPD
Subject: Prot-Amend4-208090-sponsign

Dear Sponsor,

To approve the clinical protocol indicated below, reply to this email and state your approval.

PROTOCOL NUMBER: 208090

DOCUMENT IDENTIFIER: 2017N331008_06

AMENDMENT NUMBER: 04PROTOCOL TITLE: A Phase III, randomized, multicenter, open-label, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir/lamivudine fixed dose combination in HIV-1 infected adults who are virologically suppressed

Name of Sponsor Signatory:	Sherene Shakib Min, MD, MPH
Title of Sponsor Signatory:	Vice President and Head of Clinical Development, ViiV Healthcare

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Protocol Amendment 04	*05-MAY-2020*	*2017N331008_06*
Protocol Amendment 03/SWE-DEN-1	*29-JUL-2019*	*2017N331008_05*
Protocol Amendment 03/CHI-1	*31 -MAY-2019*	*2017N331008_04*
Protocol Amendment 03	*25-MAR-2019*	*2017N331008_03*
Protocol Amendment 02	*14-NOV-2018*	*2017N331008_02*
Protocol Amendment 01	*26-MAR-2018*	*2017N331008_01*
Original	*25-JAN-2018*	*2017N331008_00*

Amendment 04, 05-MAY-2020

Overall Rationale for the Amendment: A global amendment, applicable to all participating countries (updates from global protocol amendment 04 will be incorporated into a country specific amendment for China, called 208090 Amendment 04/CHI-1). This amendment describes possible changes in patient management related to the impact of COVID-19, COVID-19 case definition guidance, ending recruitment due to COVID-19 before the original sample size was achieved and sample size considerations and statistical analyses updates. Additionally, the list of prohibited medications was updated to add fampridine to align with the Investigator Brochure version 13 and other administrative updates were made to provide updated information, correct errors and improve accuracy and consistency.

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page	Updated authors	To reflect authors of current amendment
Sponsor Signatory	Updated Sponsor signatory name and title	To align with ViiV organizational updates
Section1.1, Synopsis	Added text to clarify that the study will limit the enrolment of participants with current or prior exposure to DTG to approximately 20%.	To add clarity in the Synopsis in order to align with protocol section 4.2
Section 1.1, Synopsis Section 1.2, Schema Section 1.3, Schedule of Activities Section 4.1, Overall Design	Added text that continuation phase is not applicable for Sweden and Denmark	To clarify country specific requirements for Sweden and Denmark in the body of the

Section # and Name	Description of Change	Brief Rationale
Section 4.3, Participant and Study Completion Section 6.8, Treatment after the end of the Study		protocol to align with Appendix 13
Section 1.1, Synopsis Section 4.1, Overall Design Section 4.2, Number of Participants Section 4.4, Scientific Rationale for Study Design Section 9, Statistical Considerations	Updated statistical hypotheses and sample size determination.	The COVID-19 pandemic of 2019/2020 occurred during screening resulting in planned enrolment being terminated when approximately 445 participants were randomized and 53 were in screening
Section 1.3, Schedule of Activities Section 8, Study Assessments and Procedures	Updated table and footnote	To clarify when menopause history data will be collected
Section 1.3, Schedule of Activities Section 11.7, Appendix 7: Clinical Laboratory Tests	Added creatine phosphokinase to the list of labs collected as part of clinical chemistry in Appendix 7, footnote included in Schedule of Activities to refer to Appendix 7 and other footnote letters adjusted accordingly	To allow for collection of this lab in addition to the other liver chemistry tests already collected
Section 2, Introduction	Summary of TANGO Week 48 data added	To provide data that has become available since the prior amendment version
Section 2.3.1, Risk Assessment	Added text to describe fampridine risk and updated results from the Botswana birth outcome surveillance study for DTG and neural tube defects	To provide new information from the updated Investigator Brochure version 13
Section 4.3, Participant and Study Completion	Added text	To aid clarity
Section 6.5,	Added reference to COVID-19 appendix 14	To link appendix 14 to the main

Section # and Name	Description of Change	Brief Rationale
Preparation/Handling/Storage/Accountability Section 7.1.1.1, Participants Meeting Virologic Management Criteria Section 8, Study Assessments and Procedures Section 8.2.4, Clinical Safety Laboratory Assessments Section 8.3, Adverse events (AE) and serious adverse events (SAEs) Section 11.7, Appendix 7: Clinical Laboratory Tests		body of the protocol
Section 6.8, Treatment after the end of the study	Removed text, Added text	To correct an administrative error and to aid clarity
Section 10, References	Added references	To reflect new text added to the amendment
Section 11.6, Appendix 6, Prohibited Medications	Added fampridine and related text and clarifications	To align with current Investigator Brochure version 13 and aid clarity
Section 11.9.1, Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments	Added laboratory assessments	To align with updated guidance
Section 11.13, Appendix 13: Country-specific Requirements	Added new sections to describe previous country specific amendments for Sweden/Denmark and China. Sweden/Denmark will now be incorporated into this global amendment.	To consolidate Sweden/Denmark into the global amendment and provide clarity on past country specific protocol amendments
Section 11.14, Appendix 14: COVID-19 Pandemic and Clinical Trial Continuity	Added appendix	To summarize COVID-19 related patient management updates that were previously communicated in a memo to investigators

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase III, randomized, multicenter, open-label, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir/lamivudine fixed dose combination in HIV-1 infected adults who are virologically suppressed

Short Title: A Phase III, randomized, multicenter, open-label, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir/lamivudine fixed dose combination in HIV-1 infected adults who are virologically suppressed

Rationale: This study is being conducted to establish if adults living with human immunodeficiency virus type 1 (HIV-1) with virologic suppression on a ≥3 drug current antiretroviral regimen (CAR) remain suppressed upon switching to dolutegravir/lamivudine (DTG/3TC) fixed-dose combination (FDC). This study will also provide important information regarding the safety and health related quality of life with this two-drug regimen. This trial is designed to demonstrate the non-inferior antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks in virologically suppressed adults living with HIV-1	Virologic failure endpoint as per Food and Drug Administration (FDA) snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks	Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the intent-to-treat exposed (ITT-E) population
To evaluate the antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 24 weeks	• Virologic failure endpoint as per FDA snapshot category at Week 24 • Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG/3TC FDC once daily compared to continuation of CAR	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell counts ratio at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) through Weeks 24 and 48
To evaluate the safety and tolerability of DTG/3TC FDC once daily compared to CAR over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs
To evaluate the safety and tolerability of DTG/3TC FDC once daily in those with creatinine clearance of between 30-49 mL/min/1.73m^2 compared to those with a creatinine clearance of $\geq$50 mL/min/1.73m^2	• Incidence and severity of AEs and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs
To evaluate the effects of DTG/3TC FDC once daily on fasting lipids over time compared to CAR	Change from Baseline in fasting lipids at Weeks 24 and 48
To assess viral resistance in participants meeting Confirmed Virologic Withdrawal (CVW) Criteria	Incidence of observed genotypic and phenotypic resistance to antiretrovirals (ARVs) for participants meeting CVW Criteria

Objectives	Endpoints
To assess health related quality of life for participants treated with DTG/3TC FDC compared to CAR	Change from Baseline in health status using HIV treatment satisfaction questionnaire (HIV TSQ) at Weeks 24 and 48 (or Withdrawal from the study) and symptom distress module (SDM) at Weeks 24, 48 and every 24 weeks during the continuation phase (or Withdrawal from the study)

Overall Design:

This is a 52-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of switching from CAR to DTG/3TC FDC in adults living with HIV who are virologically suppressed and stable on CAR. The study will include a Screening Phase (up to 28 days), a Randomized Phase up to Week 52, and a Continuation Phase (post Week 52) (Section 1.2). The Continuation Phase is not applicable for participants in Sweden and Denmark. Approximately 490 adults living with HIV who are on a stable CAR will be randomized 1:1 to switch to DTG/3TC FDC once daily for up to 52 weeks, or to continue their CAR for 52 weeks. To control for treatment related factors that may impact study outcomes, randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). For participants randomized to CAR, provisions will be in place, as needed and after discussion with the study team, to assist participants in obtaining CAR during the study.

The primary endpoint for the study is the virologic failure endpoint as per FDA Snapshot category at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last participant has had their Week 48 viral load assessed, including any retests. Participants randomized to DTG/3TC FDC will receive DTG/3TC FDC up to Week 52.

All participants in the DTG/3TC FDC arm who successfully complete up to 52 weeks of treatment will have the opportunity to continue receiving DTG/3TC FDC once daily in a Continuation Phase (See Section 4.3). The Continuation Phase is not applicable for participants in Sweden and Denmark.

CVW Sub-study: A sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or Precautionary Virologic Withdrawal (PVW) Criteria will be conducted. Details are provided in Section 11.2.

Disclosure Statement: This is a parallel-group treatment study with two arms that is open-label.

Number of Participants: Assuming 20% screen failure rate, approximately 622 adult participants living with HIV will be screened to achieve approximately 490 randomized

participants for a total of 245 evaluable participants per treatment group (See Section 9.3).

A goal of this study is to enroll populations who are underrepresented in clinical studies including 20% women and approximately 20% of participants who are ≥50 years of age. Another goal is to enroll approximately 20% of participants taking efavirenz/emtricitabine/tenofovir disoproxil fumarate. The study will limit the enrolment of participants with current or prior exposure to DTG to approximately 20%.

Intervention Groups and Duration: The study will include a Screening Phase (up to 28 days), a Randomized Phase up to Week 52, and a Continuation Phase (post Week 52) (Section 1.2). The Continuation phase is not applicable for participants in Sweden and Denmark. Participants will be randomized 1:1 to switch to DTG/3TC FDC once daily for up to 52 weeks, or to continue their CAR for 52 weeks. To control for treatment related factors that may impact study outcomes, randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]).

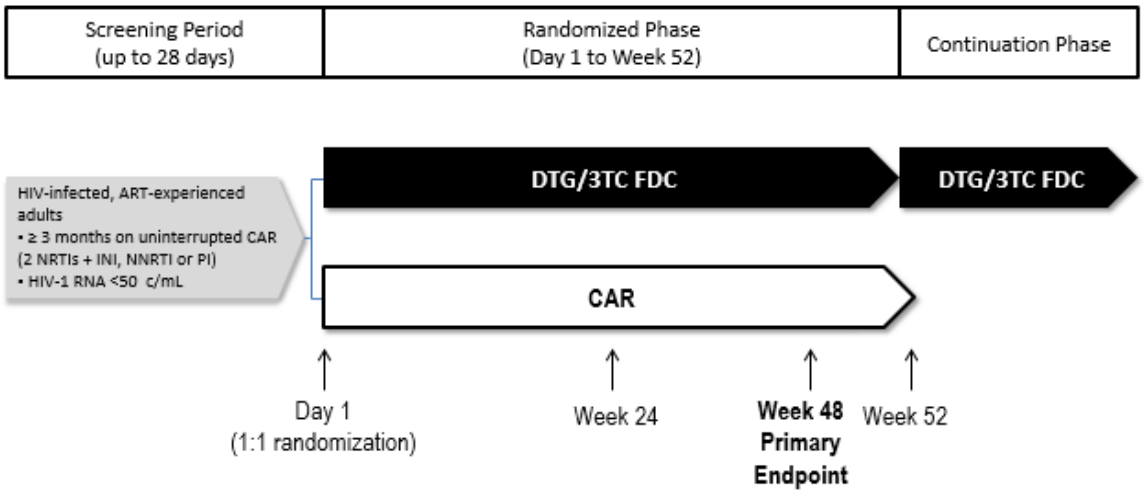
All participants in the DTG/3TC FDC arm who successfully complete up to 52 weeks of treatment will have the opportunity to continue receiving DTG/3TC FDC once daily in a Continuation Phase (See Section 4.3). Participants in the CAR arm will complete the study at Week 52. The Continuation Phase is not applicable for participants in Sweden and Denmark.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study with the exception of a switch from a PI boosted with ritonavir to the same PI boosted with cobicistat and vice versa. A switch from lamivudine to emtricitabine and vice versa is also permitted. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be communicated promptly to the study medical monitor.

Independent Data Monitoring Committee (IDMC): An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy to protect the ethical interests and well-being of participants and to protect the scientific validity of this study.

1.2. Schema

Figure 1 Study Schematic



Note: The Continuation Phase is not applicable for participants in Sweden and Denmark.

1.3. Schedule of Activities (SoA)

Procedures	Screening Visit[a]	Randomized Phase							Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline/ Day 1	4	12	24	36	48[b]	52	Every 12 Weeks After Week 52		
Clinical and Other Assessments											
Written informed consent	X										
Inclusion/Exclusion criteria[e]	X	X									
Demography	X										
Prior ART history	X										
Medical history[f]	X										
Menopause history[g]	X	X						X		X	
Current medical conditions	X										
Cardiovascular risk assessment including vital signs[h]	X										
Body Weight (BMI will be calculated within the eCRF)[i]	X	X	X	X	X	X	X	X	X	X	X
HIV risk factors and mode of transmission		X									
CDC HIV-1 classification	X	X									
HIV associated conditions[j]		X	X	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale		X[k]	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam[l]	X	X	X	X	X	X	X		X	X	X
12-lead ECG[m]	X										
Adverse events		X	X	X	X	X	X	X	X	X	X
Serious adverse events	X[n]	X	X	X	X	X	X	X	X	X	X

Procedures	**Screening Visit[a]**	**Randomized Phase**							**Continuation Phase[c]**	**Withdrawal**	**Follow-up[d]**
		Baseline/ Day 1	**4**	**12**	**24**	**36**	**48[b]**	**52**	**Every 12 Weeks After Week 52**		
Willingness to Switch[o]		X[o]									
HIV TSQ[p]		X	X		X		X			X	
Symptom Distress Module[p]		X	X		X		X		X (every 24 weeks)	X	
Laboratory Assessments											
Quantitative plasma HIV-1 RNA[q]	X	X	X	X	X	X	X		X	X	
Lymphocyte subset[r]	X	X	X	X	X	X	X			X	
Plasma for storage[s]	X	X	X	X	X	X	X		X	X	
Clinical chemistry[t]	X	X	X	X	X	X	X			X	X
Hematology	X	X	X	X	X	X	X			X	X
PT/INR (for Child-Pugh)	X										
Fasting lipids and glucose[u]		X			X		X			X[v]	
Urinalysis and spot urine for protein analysis[w]		X			X		X			X	X
Pregnancy test[x, y]	S	U/S[z]	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, Anti-HBs, and HBV DNA[aa]	X										
HCV antibody	X										
RPR	X										
Renal, bone and inflammatory marker analytes (blood/urine) and HbA1c, insulin and glucose[bb]		X			X		X			X	
Whole Blood (Virology)[cc]		X					X			X	
Whole Blood (Telomere Length)[dd]		X					X			X[ee]	

Procedures	**Screening Visit[a]**	**Randomized Phase**							**Continuation Phase[c]**	**Withdrawal**	**Follow-up[d]**
		Baseline/ Day 1	**4**	**12**	**24**	**36**	**48[b]**	**52**	**Every 12 Weeks After Week 52**		
PBMCs[ff]		X			X		X			X[gg]	
Study Treatment											
IVRS/IWRS[hh]	X	X	X	X	X	X	X	X	X	X	X
Dispense IP		X	X	X	X	X	X	X	X		
IP accountability (pill counts)			X	X	X	X	X		X	X	

ART - antiretroviral therapy, BMI - body mass index, CDC - centers for disease control and prevention, DNA - deoxyribonucleic acid, ECG – electrocardiogram, eCRF - electronic case report form, HBV – hepatitis B virus, HCV – hepatitis C virus, INR - international normalized ratio, IP - investigational product

a. As soon as all Screening results are available, randomization may occur.
b. Participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (primary endpoint) must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, occurring prior to Week 52.
c. All participants on the DTG/3TC FDC arm who complete through Week 52 will have the opportunity to enter the Continuation Phase. The Continuation Phase is not applicable for participants in Sweden and Denmark. For participants who will not continue past Week 52, do not dispense study intervention. Participants completing the Continuation Phase must return to the clinic for an End of Continuation Phase visit when transitioning to commercial supplies or to an alternate ART regimen, if appropriate. At this visit, conduct study assessments as specified for all Continuation Phase visits except for dispensing study intervention.
d. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study intervention for participants with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant. However, the investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up
e. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1. Genotypic resistance testing results if available MUST be provided to ViiV after screening and before randomization.
f. Full medical history will be conducted prior to randomization and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
g. Menopause history will include date of last menstrual period (collected at Day 1, Week 52 or withdrawal) and menopausal status (collected at Screening, Week 52 or withdrawal) based on the criteria in Section 11.4.1. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

h. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. BMI will be calculated within the eCRF.
i. The same scale should be used to measure body weight at each visit.
j. Based on the participant's current CDC status in the past 6 months.
k. On Day 1, the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS), participant completed questionnaire is to be administered prior to the first dose.
l. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
m. A 12-lead ECG will be performed in a semi-supine position after resting for at least 5 minutes.
n. Only SAEs related to study participation or to a concomitantly administered ViiV/GSK product will be collected between obtaining informed consent and administration of study intervention at Day 1.
o. Willingness to Switch Survey must be done prior to randomization.
p. Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week 48, except the Symptom Distress Module which should also be collected if Withdrawal occurs during the Continuation Phase.
q. See Virologic Withdrawal and Stopping Criteria Section of protocol (Section 7.1.1).
r. Lymphocyte subset will include collection of CD4 and CD8 for calculation of Cd4:CD8 ratio. CD8 will also be reported to sponsor.
s. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when participants meet Suspected and Confirmed Virologic Withdrawal criteria.
t. See Appendix 7 for a list of clinical chemistry labs.
u. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
v. Collect fasting lipids and glucose if the Withdrawal visit occurs at Weeks 24 or 48.
w. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
x. Women of childbearing potential only. S=serum, U=urine. Pregnancy events will be captured starting at Day 1 following exposure to study intervention.
y. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
z. Local Pregnancy result must be available **prior to randomization** on Day 1. Local serum pregnancy test on Day 1 is allowed if it can be done, and results obtained, within 24 hours **prior to randomization.**
aa. HBV DNA testing will be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Participants must return to the clinic to provide a sample for HBV DNA testing prior to randomisation.
bb. Blood sample for HbA1c, insulin, glucose, renal, bone and inflammation biomarker assessments**: Renal:** Cystatin C, Beta-2-Microglobulin (urine), Retinol Binding Protein (RBP; urine), urine B2M/creatinine ratio, urine RPB/creatinine ratio, urine albumin/creatinine ratio, urine protein/creatinine ratio, urine phosphate, serum creatinine; **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin; **Inflammation:** Interleukin-6 (IL-6), High-sensitivity C reactive protein (hs-CRP), D-dimer, Soluble CD14 (sCD14), Soluble CD163 (sCD163); insulin and glucose for HOMA-IR calculation
cc. Where local country or laboratory practices allow, whole blood (Virology) may be used for virologic analyses as described in the protocol.
dd. Where local country or laboratory practices allow, whole blood will be used for telomere length evaluation.
ee. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 48.
ff. Where local country or laboratory practices allow, PBMC collection samples may be used for virologic analyses as described in Section 8.10.1.
gg. Collect sample only if Withdrawal visit occurs at Weeks 24 or 48.

hh. At Screening, a subject number will be generated.

2. INTRODUCTION

Current human immunodeficiency virus (HIV) treatment guidelines recommend antiretroviral therapy (ART) regimens consisting of two nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs) as a "backbone" combined with a third agent from the integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (ritonavir-boosted) (PI/RTV) classes [BHIVA, 2016; DHHS, 2018; EACS, 2017; Gunthard, 2016]. These regimens are highly efficacious, generally well tolerated, and have led to remarkable declines in morbidity and mortality in people living with HIV. However, since these regimens will need to be taken life-long, there is growing concern about their long-term toxicities and cost. Lifelong ART has been associated with higher rates of non-acquired immune-deficiency syndrome (AIDS)-defining events (NADEs) such as cardiovascular disease, liver disease and cancer. In addition, as people living with HIV live longer, aging-associated co-morbidities are being seen with greater frequency, and this multi-morbidity often requires concomitant use of other medications. As the potential for toxicities and cost are directly related to the number of antiretrovirals (ARVs) used, there is great interest from people living with HIV and clinicians in regimens that minimize ARV-related long-term toxicities and drug-drug interactions (DDIs) without sacrificing long-term antiviral efficacy.

Improvements in the clinical efficacy and safety profiles of new ARV drugs have enabled the consideration of two-drug regimens as replacements for ≥3-drug ART regimens to streamline therapy and potentially minimize ARV-related long-term toxicities from cumulative drug exposures and DDIs. Improvements in tolerability may have a big impact on adherence to life-long treatment regimens. Additionally, the preservation of future ARV options and the lower cost associated with taking one less drug for the lifetime of a person living with HIV may have substantial individual and societal cost benefits.

The 2-drug regimen, dolutegravir/lamivudine (DTG/3TC) fixed dose combination (FDC), has a robust antiviral activity, safety profile, high barrier to resistance, low potential for DDIs, and can be administered as a once-daily single tablet regimen (STR). Emerging data supports DTG/3TC FDC as a viable option for both ART-experienced and naive people living with HIV-1.

LAMIDOL, a single-arm open-label study (n=110), evaluated a switch from suppressive first-line ART to DTG/3TC FDC [Joly, 2017]. Participants initially switched the third agent in their regimen to DTG (50 mg once daily) for 8 weeks, then (if HIV RNA remained <50 copies/millilitre (c/mL)) switched from 2 NRTIs to 3TC. 97% of participants who switched to 2-drug therapy maintained viral suppression after 40 weeks. Three participants had HIV RNA >50 c/mL; none of these had INSTI mutations, one had an NRTI mutation.

ASPIRE, an open-label, randomized, multicentre pilot study (n=89), evaluated a switch from 3 drug regimens (cART) to DTG + 3TC. In the primary analysis at week 24, treatment failure occurred in 3 of 44 (6.8%) receiving DTG/3TC and 3 of 45 (6.7%) receiving cART (0.15% difference; 90% CI, −9.8 to 10.2), demonstrating noninferiority

of DTG/3TC. The only participant with virologic failure (VF) (DTG/3TC arm at week 24) had no emergent RT or integrase resistance mutations, and this participant remained viremic after switching to darunavir-cobicistat plus abacavir-3TC. Using the FDA snapshot algorithm, VL was <50 copies/mL at week 24 in 41 of 44 participants in the DTG/3TC arm (93.2%) versus 41 of 45 (91.1%) in the cART arm (difference, 2.1%; 95% CI, 11.2%–15.3%; P = .71); and at week 48 in 90.9% versus 88.9% (difference 2.0%; 95% CI, −12.6% to 16.5%; P = .76) [Taiwo, 2018].

An investigator-initiated 48-week pilot study, the PADDLE trial (NCT02211482), has provided data on the efficacy of a once-daily DTG/3TC FDC 2-drug regimen for 20 HIV treatment-naïve participants with no genotypic resistance to 3TC and a viral load of <100,000 c/mL at Screening. In this study, participants were enrolled in two separate groups of 10, allowing close evaluation of response while employing a set of stopping rules with intensive follow-up in each cohort. By Week 8, all 20 participants, including 4 participants with a Baseline HIV-1 RNA of >100,000 c/mL, had reached a viral load <50 c/mL [Figueroa, 2015]. At Week 48, 18 participants (90%) reached the primary endpoint of a plasma viral load <50 c/mL [Cahn, 2017]. The regimen was well tolerated and no toxicity issues were observed. All 18 participants who completed 48 weeks were included in an extension phase up to Week 96. At Week 96, all 18 participants maintained plasma viral load <50 c/mL [Figueroa, 2017].

Data from larger studies is available from two ongoing Phase III trials (GEMINI-1 and -2) in naive participants. 714 and 719 adults were randomised and treated in GEMINI-1&2, respectively. Based on a 10% non-inferiority margin, DTG+3TC was non-inferior to DTG+TDF/FTC at Week 48 in both GEMINI-1&2 and in the pooled analysis. Response rates in participants with baseline HIV-1 RNA >100,000 c/mL were high and similar between arms. Across both studies, 6 participants on DTG+3TC and 4 on DTG+TDF/FTC met protocol-defined virologic withdrawal criteria through Week 48; none had treatment-emergent primary integrase-strand transfer inhibitor or NRTI resistance mutations. Overall rates of AEs were similar between arms, with low rates of withdrawals due to AEs for both DTG+3TC and DTG+TDF/FTC. More drug related AEs were reported with DTG+TDF/FTC [Cahn, 2018]. Data is also available from a third ongoing Phase III trial (TANGO) in ART-experienced participants. 743 adults were enrolled and 741 received ≥1 dose of study drug (DTG/3TC, N=369; TAF-based regimen, N=372). At Week 48, proportion of participants with HIV-1 RNA ≥50 copies/mL treated with DTG/3TC was 0.3% (1/369) vs 0.5% (2/372) with a TAF-based regimen (adjusted treatment difference [95% CI], −0.3 [−1.2, 0.7]), meeting non-inferiority criteria. No participants receiving DTG/3TC and 1 receiving a TAF-based regimen met confirmed virologic withdrawal criteria, with no emergent resistance at time of failure. Drug-related grade ≥2 adverse events and adverse events leading to study withdrawal were reported in 17 (4.6%) and 13 (3.5%) participants with DTG/3TC and 3 (0.8%) and 2 (0.5%) with a TAF-based regimen, respectively.

2.1. Study Rationale

This study is being conducted to establish if adults living with HIV-1 with virologic suppression on a ≥3 drug current antiretroviral regimen (CAR) remain suppressed upon switching to DTG/3TC FDC. This study will also provide important information regarding the safety and health related quality of life with this two-drug regimen. This

trial is designed to demonstrate the non-inferior antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks.

DTG/3TC FDC may provide an effective and well-tolerated two-drug regimen for ART-experienced people living with HIV, limiting the risk of many common adverse reactions associated with other ARV drugs. This regimen could be particularly valuable for people with co-morbid conditions such as bone or cardiovascular disease, and in resource-limited settings due to DTG's known efficacy advantages and both drugs' tolerability and long-term safety profiles, as well as ease of use (once daily dosing, no food dosing effects/requirements, and limited potential for DDIs). The expected efficacy and safety of DTG/3TC FDC will make it suitable for both treatment-naïve individuals and as a replacement treatment for ≥3-drug ART in virologically suppressed ("switch") participants.

By limiting the number of ARV's to which a participant is chronically exposed, 2-drug therapy has the potential benefit of preserving future treatment options, minimizing potential long-term toxicity and decreasing the likelihood of DDIs. These benefits could have a large impact on tolerability and adherence and thus prevent drug resistance.

2.2. Background

FDCs and STRs have greatly simplified the treatment of people living with HIV, and may be of greater importance in people with lifestyles or care commitments that may impair adherence to dosing schedules, including some women and those in underserved populations. In a study by Paterson et. al. [Paterson, 1999], a linear relationship between levels of adherence and viral load suppression was observed. Adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and people living with HIV-1 who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most people who struggle with consistent adherence. To achieve successful long-term treatment, the prevention of drug resistance has become the most significant challenge.

DTG is a potent dual cation binding INSTI, exhibiting rapid reduction in viral load, best in class efficacy, and a high barrier to resistance. These properties and its safety profile make it an optimal core agent for 2-drug regimens. In addition, due to its mechanism of metabolism, DTG lacks many of the frequent DDIs associated with other medications commonly taken by people living with HIV. To date, the efficacy, pharmacokinetics (PK), safety and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to IIIB clinical trials [TIVICAY Package Insert, 2017; GlaxoSmithKline Document Number RM2007/00683/11; GlaxoSmithKline Document Number 2017N352880_00; GlaxoSmithKline Document Number 2017N352880_01].

3TC is a potent cytidine nucleoside analogue without major side effects and has a well proven safety profile. Available since 1995 as a single agent (EPIVIR) [EPIVIR Package Insert, 2017], it is also available as part of three FDC products (zidovudine (ZDV)/3TC, COMBIVIR, abacavir (ABC)/3TC, EPZICOM/KIVEXA, ABC/3TC/DTG, TRIUMEQ). 3TC monotherapy is known to select for resistance due to a single point mutation that

reduces antiviral activity. However, it is predicted that 3TC, when combined with DTG with its high barrier to resistance and ability to confer a very rapid decline in HIV-1 RNA, may be less likely to select for resistance consistent with clinical studies combining DTG, 3TC and ABC [Walmsley, 2013; Walmsley, 2015; Cahn 2018].

Chronic exposure to NRTIs may lead to telomerase and mitochondrial dysfunction, processes that may lead to accelerated aging, lipodystrophy, steatohepatitis and other aging-related morbidities [Solomon, 2014]. NRTIs have been linked to reduced telomerase activity in peripheral blood mononuclear cells (PBMCs) from people living with HIV [Leeansyah, 2013]. Of a multitude of NRTIs studied in vitro, tenofovir at therapeutic concentrations produced the most significant inhibition of telomerase leading to accelerated shortening of telomere length in activated PBMCs [Leeansyah, 2013; Stella-Ascariz, 2017]. It is of note that current tenofovir alafenamide (TAF)-regimens deliver four-fold higher intracellular levels of tenofovir-diphosphate (the active entity for both HIV- reverse transcriptase (RT) and human telomerase) than TDF-regimens and thus pose a greater concern for its effects on telomerase and normal cell proliferation. In addition, many of the current TAF-based single tablet regimens incorporate a boosting agent, cobicistat, while PI-containing regimens require boosting with ritonavir. The use of cobicistat- and ritonavir-containing regimens further increase the risk of potential DDIs from polypharmacy.

One of the potential risks of a two-drug regimen, such as DTG/3TC FDC, is the increase in virologic failure associated with the emergence of resistance. DTG, with its higher barrier to resistance, may reduce treatment-emergent resistance in participants taking a two-drug regimen. The overall efficacy data from the pivotal Phase III studies of DTG in ART-naïve participants are extensive, with no resistance mutations being identified through 144 weeks of treatment (SINGLE, ING114467) [Walmsley, 2015]. The absence of treatment-emergent mutations to DTG or background agents in ART-naïve individuals, rapid virologic response demonstrated for DTG-based regimens, and the *in vitro* potency and well-tolerated safety profile of both DTG and 3TC all provide a strong rationale for the development of a DTG/3TC STR as a treatment option for people living with HIV.

Several studies have demonstrated the tolerability and durability of the virologic response of a 2-drug ARV regimen as replacement for a ≥3-drug ARV regimen in individuals who were previously suppressed on triple drug therapy.

One such study was the *Only Lopinavir and Epivir* (OLE) study which was an open-label study in 250 virologically suppressed individuals living with HIV (HIV-1 RNA <50 c/mL) receiving a lopinavir (LPV)/r plus 3TC or emtricitabine (FTC) containing 3-drug regimen who were randomized to continue their current triple based regimen or have their therapy simplified to a 2-drug regimen of LPV/r + 3TC [Arribas, 2015]. The primary endpoint was the proportion of participants free of therapeutic failure at 48 weeks. In a modified Intent to Treat (m-ITT) analysis, 2-drug therapy with LPV/r + 3TC demonstrated non-inferior efficacy and comparable safety to LPV/r + 2 NRTIs, as maintenance therapy in virologically suppressed participants (91.5% vs. 90.9% respectively; 95% Confidence Interval (CI): -0.6% to 8.1%).

The *Simplification to Atazanavir/Ritonavir+Lamivudine as Maintenance Therapy* (SALT) study [Perez-Molina, 2015] was a 96-week multicenter, randomized, open-label, clinical trial that compared atazanavir/ritonavir (ATV/r) + 3TC with ATV/r + 2NRTIs (selected at the discretion of the investigator) in 286 people living with HIV on a stable 3-drug regimen who switch therapy because of toxicity, intolerance, or simplification. The primary endpoint was to evaluate the non-inferior efficacy of maintenance therapy with ATV/r + 3TC compared to ATV/r + 2 NRTIs at 48 weeks (noninferiority margin, –12%) using the time to loss of virologic response (TLOVR) algorithm. At 48 weeks, 78.4% of participants receiving triple therapy vs. 83.6% of participants switched to 2-drug therapy had maintained HIV-RNA levels <50 c/mL thus establishing non-inferiority between these two treatment arms (difference between the arms 5.2; -4.8 to 15.2). Treatment discontinuations (2%) were less frequent in the 2-drug therapy group (vs 7% in the triple therapy group).

An INSTI-containing oral 2-drug regimen, cabotegravir (CAB) + rilpivirine (RPV), was evaluated as a maintenance therapy in people living with HIV who had virologic suppression after 24 weeks of 3-drug ART [Margolis, 2015]. The CAB + RPV arms showed comparative antiviral efficacy as the efavirenz (EFV) + 2 NRTIs arm. Following 72 weeks of two-drug maintenance therapy (Week 96), in the ITT maintenance = exposed population, 86% of CAB + RPV participants and 83% of EFV + 2 NRTIs participants remained virologically suppressed. Virologic failure was seen in 4% of the CAB arm and 2% of the EFV+2 NRTI arm.

The SWORD-1 and SWORD-2 studies [Llibre, 2017] are ongoing 148-week open-label, multicenter Phase III, non-inferiority studies evaluating the efficacy and safety of switching from a 3 or 4-drug current antiretroviral regimen (CAR) to DTG + RPV in 1024 participants. The primary endpoint was the proportion of participants with plasma HIV-RNA levels <50 c/mL at Week 48. Switching to DTG + RPV was found to be non-inferior to continuing CAR in pooled analysis of both the intent-to-treat exposed (ITT-E) population [95% vs. 95%; difference: -0.2% (95% CI: -3.0%, 2.5%)] and the per-protocol population [96% vs. 96%; difference: -0.7% (95% CI: -3.3%, 1.8%)]. For the pooled studies, 23% and 21% of participants were female in the DTG +RPV and CAR arms, respectively. Efficacy remained high in the female subgroup (93% vs. 91%). At Week 100 in the Early Switch group, 456 (89%) had VL < 50c/mL; low rate of snapshot virologic non-response was observed (3%); 6 (1.2%) participants met Confirmed Virologic Withdrawal (CVW) criterion. One participant with RPV resistance at CVW (Early Switch group, Wk100) had pre-existing NNRTI mutations at baseline. No participants developed INSTI resistance [Aboud, 2018].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of DTG or 3TC may be found in the most recent version of the Investigator's Brochure (IB) and any IB supplements and the product labels.

The following section outlines the risk assessment and mitigation strategy for DTG and 3TC in this protocol. For CAR, the approved country product labels for the respective drugs should be referenced.

2.3.1. Risk Assessment

The following table outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to Investigator Brochures (IBs) for additional information		
DTG: Hypersensitivity reaction (HSR) and rash	**DTG:** HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	Participants with history of allergy/sensitivity to any of the study interventions are excluded. Specific/detailed toxicity management guidance is provided for rash (Section 11.3.1.6). The participant informed consent form (ICF) includes information on this risk and the actions participants should take in the event of a HSR or associated signs and symptoms
DTG: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations **3TC**: Use in HBV co-infected participants and emergence of HBV variants resistant to 3TC	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For participants with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART, along with inadequate therapy for HBV co-infected participants, likely contributed to significant elevations in liver chemistries. A review of postmarketing data found that the number of cases reporting particularly severe liver dysfunction was found to be very low in the context of exposure to DTG and DTG/ABC/3TC. The reported cases of severe liver dysfunction (including acute hepatic failure) are complex with potential confounding factors but in a very small number of cases, drug-induced liver injury is likely and the role of DTG containing regimens cannot be ruled out particularly in those involving DTG	Participants meeting any of the following criteria during the screening period are excluded from participating. • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin) • Participants positive for Hepatitis B surface antigen (+HBsAg) • Participants negative for HBsAg and anti-HBsAg and positive for anti-HBc and HBV DNA • Anticipated need for any hepatitis C virus (HCV) therapy during the randomized phase of the study, or anticipated need for HCV therapy with a potential for adverse drug-drug interactions with DTG or 3TC Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 11.9).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to Investigator Brochures (IBs) for additional information		
	with ABC/3TC or DTG/ABC/3TC. **3TC**: Current treatment guidelines [DHHS, 2018; EACS, 2017] do not recommend monotherapy with 3TC for participants with HBV infection, which is what participants randomised to DTG/3TC FDC, would effectively be receiving. Emergence of HBV variants associated with resistance to 3TC has been reported in HIV-1-infected participants who have received 3TC-containing antiretroviral regimens in the presence of concurrent infection with HBV. Additionally, discontinuation of 3TC in HBV co-infected participants can result in severe exacerbations of hepatitis B.	
DTG: Psychiatric disorders	**DTG:** Psychiatric disorders including suicidal ideation and behaviours are common in people living with HIV. Events of suicidal ideation, attempt, behaviour and completion were observed in clinical studies of DTG, primarily in participants with a pre-existing history of depression or other psychiatric illness. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favourable compared with EFV- based regimens. The reporting rate for insomnia was statistically higher for blinded DTG+ abacavir/lamivudine (ABC/3TC) compared to EFV/TDF/FTC in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG.	Participants who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating. Because of the elevated risk in the population of people living with HIV, treatment emergent assessment of suicidality will be monitored during this study through the end of the continuation phase. Investigators are advised to consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour (See Section 8.2.5). The participant informed consent form includes information on the risk of depression and suicidal ideation and behaviour.
DTG: Increased rates of virologic failure/	Virologically suppressed participants switching from stable ART to DTG/3TC FDC may experience virologic failure/breakthrough and	Participants with any switch to a second line regimen due to previous virologic failure and participants with evidence of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to Investigator Brochures (IBs) for additional information		
Observed Resistance	development of resistance. **DTG:** Week 96 and Week 144 analyses for the Phase III/IIIb clinical studies supported the efficacy findings from earlier analyses, and demonstrated robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve participants. **3TC**: M184V is the common single mutation that leads to full resistance to 3TC.	pre-existing viral resistance mutation (including M184I/V) are excluded from this study. Genotypic resistance testing results ≧ be reviewed by ViiV Virology to ensure participants with exclusionary mutations are not randomized. Participants will have HIV-1 RNA measured at routine study visits. An independent data monitoring committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy.
DTG: Theoretical serious drug interaction with dofetilide, pilsicainide and fampridine	Co-administration of DTG may increase dofetilide/pilsicainide and fampridine plasma concentration via inhibition of organic cation transporter (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide, pilsicainide or fampridine is prohibited in the study (Section 11.6).
DTG and 3TC: Renal function	**DTG**: Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with inhibition of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. **3TC**: 3TC is eliminated by renal excretion and exposures increase in participants with renal dysfunction. 3TC is not recommended to treat participants with a creatinine clearance <50 mL/min.	Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 11.3.1.3). Creatinine clearance is calculated in all participants prior to initiating therapy and renal function (creatinine clearance and serum phosphate) will be monitored at all subsequent study visits. Participants with creatinine clearance <30 mL/min are excluded from participation in this study. Safety events, including laboratory toxicities will be monitored closely in participants with creatinine clearance between 30-49 mL/min, as outlined in the Schedule of Activities table.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to Investigator Brochures (IBs) for additional information		
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, updated results from an interim analysis show that 5/1683 (0.3%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female participant is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 4, Section 11.4.2) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and will be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected participants). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study intervention, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

b. Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (GSK)/ViiV Safety Review Team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

2.3.2. Benefit Assessment

Individually, DTG and 3TC are conveniently dosed once daily without regard to meals, without need for a PK booster, and with limited safety implications resulting from theoretical or actual DDIs compared to other ART agents (including EFV and those requiring a PK booster). In addition, the high barrier to resistance observed with DTG should help protect against the development of resistance to both components of the DTG/3TC FDC regimen. Individually, DTG and 3TC in combination with other ARVs have demonstrated durable virologic and immunologic response.

In general, switching participants to a DTG/3TC FDC regimen from a dual NRTI-based 3-drug regimen may increase tolerability, reduce the frequency of adverse events associated with NRTI-based regimens and/or DDIs. Study participants also may benefit from the medical tests and screening procedures performed as part of this study.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with DTG/3TC FDC are justified by the anticipated benefits that may be afforded to study participants switching to this 2-drug regimen.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks in virologically suppressed adults living with HIV-1	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks	Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To evaluate the antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 24 weeks	• Virologic failure endpoint as per FDA snapshot category at Week 24 • Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG/3TC FDC once daily compared to continuation of CAR	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell counts ratio at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 and 48
To evaluate the safety and tolerability of DTG/3TC FDC once daily compared to CAR over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs
To evaluate the safety and tolerability of DTG/3TC FDC once daily in those with creatinine clearance of between 30-49 mL/min/1.73m^2 compared to those with a creatinine clearance of $\geq$50 mL/min/1.73m^2	• Incidence and severity of AEs and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs

Objectives	Endpoints
To evaluate the effects of DTG/3TC FDC once daily on fasting lipids over time compared to CAR	Change from Baseline in fasting lipids at Weeks 24 and 48
To assess viral resistance in participants meeting Confirmed Virologic Withdrawal (CVW) Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for participants meeting CVW Criteria
To assess health related quality of life for participants treated with DTG/3TC FDC compared to CAR	Change from Baseline in health status using HIV TSQ at Weeks 24 and 48 (or Withdrawal from the study) and SDM at Weeks 24, 48 and every 24 weeks during the continuation phase (or Withdrawal from the study)
Exploratory	
To assess willingness to switch for participants treated with DTG/3TC FDC compared to CAR	Reasons for Willingness to Switch at Day 1
To evaluate renal (in urine and blood), bone (in blood), inflammatory (in blood) biomarkers and insulin resistance in participants treated with DTG/3TC FDC compared to CAR	Change from Baseline in renal, bone and inflammatory biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 24 and 48
To evaluate biomarkers of telomerase function in participants treated with DTG/3TC FDC compared to CAR.	Change from baseline in biomarkers of telomerase function at Week 48

4. STUDY DESIGN

4.1. Overall Design

This is a 52-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of switching from CAR to DTG/3TC FDC in adults living with HIV who are virologically suppressed and stable on CAR. The study will include a Screening Phase (up to 28 days), a Randomized Phase up to Week 52, and a Continuation Phase (post Week 52) (Section 1.2). The Continuation Phase is not applicable for participants in Sweden and Denmark. Approximately 490 adults living with HIV who are on a stable CAR will be randomized 1:1 to switch to DTG/3TC FDC once daily for up to 52 weeks, or to continue their CAR for 52 weeks. To control for treatment related factors that may impact study outcomes, randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). For participants randomized to CAR, provisions will be in place, as needed and after discussion with the study team, to assist participants in obtaining CAR during the study.

The primary endpoint for the study is the virologic failure endpoint as per FDA Snapshot category at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last participant has had their Week 48 viral load assessed, including any retests. Participants randomized to DTG/3TC FDC will receive DTG/3TC FDC up to Week 52.

All participants in the DTG/3TC FDC arm who successfully complete up to 52 weeks of treatment will have the opportunity to continue receiving DTG/3TC FDC once daily in a Continuation Phase (See Section 4.3). Participants in the CAR arm will complete the study at Week 52. The Continuation Phase is not applicable for participants in Sweden and Denmark.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study with the exception of a switch from a PI boosted with ritonavir to the same PI boosted with cobicistat and vice versa. A switch from lamivudine to emtricitabine and vice versa is also permitted. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be communicated promptly to the study medical monitor.

An Independent Data Monitoring Committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy to protect the ethical interests and well-being of participants and to protect the scientific validity of this study.

A sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or PVW Criteria will be conducted. Details are provided in Section 11.2.

4.2. Number of Participants

Assuming 20% screen failure rate, approximately 622 adult participants living with HIV will be screened to achieve approximately 490 randomized participants for a total of 245 evaluable participants per treatment group (See Section 9.3).

A goal of this study is to enrol populations who are underrepresented in clinical studies including at least 20% women and approximately 20% of participants who are ≥50 years of age. To provide sufficient data to determine whether women respond differently than male participants and whether participants who are ≥50 years of age respond differently than those < 50 years of age, sites are expected to consider women and participants ≥50 years of age in their screening strategies. Another goal of the study is to enrol approximately 20% of participants taking efavirenz/emtricitabine/tenofovir disoproxil fumarate to reflect on its continued use as first line ARV of choice in many countries. Enrolment may be allowed to continue at select sites to attempt to reach targets in these key study populations.

The study will limit the enrolment of participants with current or prior exposure to DTG to approximately 20%.

4.3. Participant and Study Completion

Participants are considered to have completed the study if they satisfy one of the following:

- Randomly assigned to either treatment group, completed the Randomized Phase including the Week 52 visit, and did not enter the Continuation Phase;

- Randomly assigned to DTG/3TC FDC, completed the Randomized Phase including the Week 52 visit, entered and completed the Continuation Phase, defined as remaining on study until:

    - DTG and 3TC are each locally approved for use as part of a 2-drug regimen, and each of the single entities of DTG and 3TC are available through public health services or through the participant's usual health insurance payer, or
    - the actual DTG/3TC FDC tablet, if required by local regulations, is available, or
    - the participant no longer derives clinical benefit, or
    - the participant meets a protocol-defined reason for discontinuation, or
    - development of the DTG plus 3TC 2-drug regimen is terminated

The Continuation Phase is not applicable for participants in Sweden and Denmark.

An in-clinic Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit. Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a

laboratory abnormality). The Follow-Up visit is not required for successful completion of the study.

4.4. Scientific Rationale for Study Design

The design of this study (1:1 randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study) is well established for confirming the non-inferiority of an investigational agent compared with an active ART standard-of-care regimen and generally is accepted by regulatory authorities as rigorous proof of antiviral activity. The primary endpoint, proportion of participants defined as virologic failures by the FDA Snapshot algorithm, is recommended in the FDA's 2015 guidance document for assessing efficacy in Switch Trials [CDER, 2015]. The key secondary endpoint, proportion of participants at Week 48 with plasma HIV-1 RNA<50 c/mL, is also a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2015].

Several studies have demonstrated the value/feasibility of a switch study design, an approach that has been shown to generate valuable data supporting ARV combinations that allow dosing flexibility, reduced toxicity and/or drug interactions or a reduction in pill burden. A simplified ARV regimen may also contribute to increased medication adherence and reduced HIV transmission. A potential disadvantage of a switch study design is that effective, well-tolerated ART is discontinued at the time of switching to the simplified regimen [Carr, 2012].

Previous studies have shown the non-inferiority of a 2-drug regimen in maintaining virologic suppression when participants who were virologically suppressed on a 3-drug regimen were switched to a 2-drug regimen (See Section 2.2).

In this study, participants will be randomized 1:1 to switch to DTG/3TC FDC from CAR at Day 1 or stay on their CAR for up to 52 weeks. The primary endpoint will be evaluated at Week 48 using a 5% non-inferiority (NI) margin. The rationale for this decision is provided in Section 9.2.1. This study is evaluating the rate of Snapshot algorithm measured virologic failure in already suppressed participants to test the hypothesis that maintenance of the suppression of HIV-1 replication by DTG/3TC FDC will be non-inferior to that observed in the CAR arm of the study through Week 48.

This study will also evaluate the safety and tolerability of this 2-drug regimen in persons with a creatinine clearance of between 30 – 49 mL/min/1.73m^2. The DTG 50mg dose is approved for persons with a creatinine clearance of as low as 30 mL/min/1.73m^2. 3TC plasma concentrations area under the curve (AUC) are increased in participants with moderate to severe renal impairment due to decreased clearance, and the current label recommends a dose of 150 mg once a day for a creatinine clearance of between 30-49 mL/min/1.73m^2. However, several randomized controlled studies that have compared a total 3TC daily dose of 600 mg/day to 300 mg/day showed only small, statistically non-significant differences between the treatment arms in the frequency of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory toxicities and withdrawals due to AEs [Eron, 1995; GlaxoWellcome Document Number UCR/95/003, 1995; GlaxoWellcome Document Number GIO/94/005, 1995]. Our study will allow

inclusion of participants with creatinine clearance of ≥30 mL/min/1.73m^2 to confirm these earlier observations. The protocol includes extensive serum and urine renal function laboratory tests collected at each study visit, and has management procedures for specified change (decrease) in renal function.

This study will aim to enrol 20% females to provide safety and efficacy data to help inform clinicians about use of this ART regimen in women. While women comprise approximately 50% of people living with HIV globally, the number of women in most HIV clinical trials remains low, and recruiting and retaining women into antiretroviral clinical studies remains a challenge. The reasons are multiple, but may reflect differences in lifestyle, care commitments, behaviour and socioeconomics between women and men living with HIV. Additionally, women may metabolize and respond to antiretroviral agents differently than men; women may have higher drug exposure, be at greater risk for some adverse events (i.e., lactic acidosis, hepatotoxicity/rash, and osteoporosis), and have an added potential for drug-drug interactions (i.e., oral hormonal contraceptives/or estrogen).

The open-label design best suits the objectives of this study. A double-dummy design could not be undertaken given the increase in pill burden that would result from blinding, the differing requirements for dosing a variety of CAR with food, and wide variety of potential DDIs. An increase in pill burden could hinder compliance substantially and discourage participant enrolment. The use of the FDA snapshot algorithm for assessing the proportion of participants with virologic failure as an objective primary endpoint will help reduce biases inherent to an open-label study design.

4.5. Justification for Dose

To date, the efficacy, PK, safety, and drug interaction potential of DTG and 3TC as individual agents have been evaluated in two extensive clinical development programs of Phase I to III clinical trials. As individual agents, DTG and 3TC are both approved and marketed as TIVICAY 50 mg once daily and EPIVIR 300 mg once daily, respectively. These doses will be used in the current study.

Comprehensive clinical studies have been conducted with the individual DTG and 3TC products, including clinical pharmacology studies evaluating potential DDIs between each of these active ingredients and other agents. There are no known clinically relevant PK interactions between DTG and 3TC with concomitant dosing.

A summary of the overall clinical development for both products is available in the most recent version of the IBs and or Product Insert(s) for the respective products [see DTG IB: GlaxoSmithKline Document Number RM2007/00683/11; GlaxoSmithKline Document Number 2017N352880_00; GlaxoSmithKline Document Number 2017N352880_01; Dolutegravir (TIVICAY) Product Insert; 2017; EPIVIR Product Insert, 2017].

Based on the preliminary results of the pivotal bioequivalence study (204994), a bilayer tablet formulation with a core which utilizes the same formulation in the respective layers as the single entity tablets was selected. When administered in the fasted state, the bilayer tablet demonstrated bioequivalence to the single entity tablets for dolutegravir area under the curve zero to infinity (AUC(0-∞)) & maximum concentration (Cmax) and

lamivudine AUC(0-∞). However, the bilayer tablet showed a modest increase in lamivudine Cmax compared to the single entity tablet, which is not considered to be clinically significant.

5. STUDY POPULATION

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product or other study interventions that may impact participant eligibility is provided in the Product Insert(s) for DTG, 3TC or CAR.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

The following are study specific eligibility criteria unless stated otherwise. In addition to these criteria, Investigators must exercise clinical discretion regarding selection of appropriate study participants, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP).

Laboratory results provided from central laboratory services will be used to assess eligibility. In exceptional circumstances only, if a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor, for consideration of participant eligibility, except for plasma HIV-1 RNA.

5.1. Inclusion Criteria

Eligible participants must:

- be able to understand and comply with protocol requirements, instructions, and restrictions;
- be likely to complete the study as planned;
- be considered appropriate candidates for participation in an investigative clinical trial with oral medication (e.g. no active problematic substance abuse, acute major organ disease, or potential long-term work assignments out of the country).

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Aged 18 years or older (or older, if required by local regulatory agencies), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Adults living with HIV

3. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening.
4. Plasma HIV-1 RNA <50 c/mL at Screening.
5. Must be on uninterrupted current regimen (either the initial or second cART regimen) for at least 3 months prior to Screening.

   Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability and/or safety concerns or access to medications, or convenience/simplification and must NOT have been done for suspected or established treatment failure. The following switches, if they are the only switches, would not be considered a change in regimen:

   a. A switch from a PI boosted with RTV to the *same* PI boosted with cobicistat is allowed (and vice versa).
   b. A switch from lamivudine (3TC) to emtricitabine (FTC) (and vice versa)
   c. A switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) (and vice versa)"

Acceptable stable cART regimens prior to Screening include 2 NRTIs plus:

- INI (either the initial or second cART regimen)
- NNRTI (either the initial or second cART regimen)
- Boosted PI (or atazanavir [ATV] unboosted) (either the initial or second PI-based cART regimen)

NOTE: Combination triple ART ≤10 days with any antiretroviral agent following a diagnosis of HIV-1 infection is not considered a prior cART regimen.

Sex

6. Male and Female

a. Female participants:

A female participant is eligible to participate if she is not pregnant [as confirmed by a negative serum human chorionic gonadotrophin (hCG) test at screen and a negative urine hCG test at Randomization (a local serum hCG test at Randomization is allowed if it can be done, and results obtained, within 24 hours prior to randomization)], not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Section 11.4.1

OR

- A WOCBP who agrees to follow the contraceptive guidance in Section 11.4.2 during the treatment period from 28 days prior to the first dose of study

medication and for at least 2 weeks after the last dose of study medication. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

All participants in the study should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 10 which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

Other

8. Participants enrolled in France must be affiliated to, or a beneficiary of, a social security category.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Concurrent Conditions/Medical History

1. Women who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study
2. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], EXCEPT cutaneous Kaposi's sarcoma not requiring systemic therapy. Historical or current CD4 cell counts less than 200 cells/mm^3 are NOT exclusionary.
3. Participants with severe hepatic impairment (Class C) as determined by Child-Pugh classification (see Section 11.5).
4. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
5. Evidence of Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antigen antibody (anti-HBs) and HBV DNA as follows:
   - Participants positive for HBsAg are excluded.
   - Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded.

Note: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded. Anti-HBc must be either total anti-HBc or anti-HBc immunoglobulin G (IgG), and NOT anti-HBc IgM. Participants with a documented history of chronic HBV and current undetectable HBV DNA while on a TAF/TDF regimen are excluded.

6. Anticipated need for any hepatitis C virus (HCV) therapy during the randomized phase of the study, or anticipated need for HCV therapy with a potential for adverse drug-drug interactions with DTG or 3TC.
7. Untreated syphilis infection (positive rapid plasma reagin [RPR] at Screening without clear documentation of treatment). Participants who are at least 7 days post completed treatment are eligible.
8. History or presence of allergy or intolerance to the study interventions or their components or drugs of their class.
9. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia.
10. Participants who in the investigator's judgment, poses a significant suicidality risk
11. Any pre-existing physical or mental condition which, in the opinion of the Investigator, may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant.
12. Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the study interventions or render the participant unable to take oral medication.

Exclusionary Treatments Prior to Screening or Day 1

13. Use of any regimen consisting of single or dual ART (peri-partum treatment with single dose nevirapine is allowed).
14. Current use of stavudine, didanosine, or nelfinavir
15. Participants receiving any prohibited medication listed in Section 11.6 and who are unwilling or unable to switch to an alternate medication
16. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening;
17. Treatment with any of the following agents within 28 days of Screening
    - radiation therapy
    - cytotoxic chemotherapeutic agents
    - any systemic immune suppressant
18. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP.

Laboratory Values or Clinical Assessments at Screening

19. Any evidence of major NRTI mutation or presence of any DTG resistance-associated mutation [Wensing, 2017] in any available prior resistance genotype assay test result, if known. Refer to the most recent version of IAS Guidelines [Wensing, 2017], SRM, and Section 8 (Screening Assessments) for more information. All resistance reports with HIV-1 reverse transcriptase or integrase genotypic data *must* be provided to ViiV after screening and before randomization for review by ViiV virology.
20. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening period to verify a result.
21. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) *or* ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).
22. Creatinine clearance of <30 mL/min/1.73m^2 via CKD-EPI method. Participants with creatinine clearance between 30 – 49 mL/min/1.73m^2 are eligible after the medical monitor has provided approval after reviewing participant's current ART regimen.
23. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator, would preclude the participant's participation in the study of an investigational compound.

Exclusionary Criteria Prior to Screening or Day 1

24. Within the 12 month window prior to Screening and after confirmed suppression to <50 c/mL, any plasma HIV-1 RNA measurement >200 c/mL.
25. Within the 12 month window prior to Screening and after confirmed suppression to <50 c/mL, 2 or more consecutive plasma HIV-1 RNA measurements ≥50 c/mL. A single plasma HIV-1 RNA measurement >50 c/mL but less than 200 c/mL, with confirmation of return to <50 c/mL is allowed.
26. Any drug holiday during the 6 months prior to Screening, except for brief periods (less than 1 month) where <u>all</u> ART was stopped due to tolerability and/or safety concerns.
27. Any history of switch to another regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA ≥400 c/mL.
28. Participants who are currently participating in or anticipate to be selected for any other interventional study after randomization (NOTE: participants who are already enrolled into another interventional study at time of screening **may** be eligible after consultation with the ViiV Healthcare/GSK study team prior to randomization. Considerations include participant's ability to attend all visits on schedule, and possible drug and study procedure compatibility). See SRM for further details.

Country Specific Requirements

29. Participants enrolled in France (or in other countries as required by local regulations or Ethics Committee/Institutional Review Board [IRB]) who:

- participated in any study using an investigational drug or vaccine during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study, or
- participate simultaneously in another clinical study.

Notwithstanding these minimum inclusion and exclusion criteria, Investigators must also follow country specific guidelines where they exist when making decisions about participants who are eligible for study participation.

5.3. Lifestyle Restrictions

This section is not applicable to this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Participants are allowed to re-screen for this study one time (except where screen HIV-1 plasma RNA ≥50 c/mL or where exclusionary HIV-1 resistance was present). Re-screening will require a new subject number.

A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility. However, a repeat HIV-1 RNA, if HIV-1 RNA was ≥50 c/mL is not allowed.

Laboratory results provided from central laboratory services will be used to assess eligibility. In exceptional circumstances only, if a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor, for consideration of participant eligibility, except for plasma HIV-1 RNA.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/retrieved during the screening period. Under no circumstances may a participant be randomized in the absence of source documentation including prior qualifying viral load data (as outlined in the Inclusion Criteria).

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study intervention may refer to the individual study interventions or the combination of those study interventions. All study interventions will be administered at the approved dosages.

The investigational study intervention DTG/3TC FDC will be supplied by ViiV Healthcare/GSK as the fixed dose combination tablet. Participants randomly assigned to continue CAR for up to 52 weeks will not have drug provided as clinical trial material, except where provision of CAR in this specific study setting is required by country and local regulations. The individual components of CAR will be recorded on the Concomitant ART Therapy (ConART) eCRF page. For participants randomized to CAR, provisions will be in place, as needed and after discussion with the study team, to assist participants in obtaining their CAR during the study.

DTG/3TC FDC must be stored in a secure area under the appropriate physical conditions for the product. Access to and dispensing of the DTG/3TC FDC will be limited to the investigator and authorized site staff. Study intervention must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol. For further details on storage, access and administration of study interventions, refer to the SRM.

6.1. Study Interventions Administered

Table 1 Study Interventions

Intervention Name:	DTG/3TC FDC	CAR
Dosage formulation:	White, oval, film-coated tablets	Refer to product label
Unit dose strength(s)/Dosage level(s):	50mg/300mg	Refer to product label
Route of Administration	oral	Refer to product label
Dosing instructions:	Take one tablet daily	Refer to product label
Packaging and Labelling	The tablets are packed in high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 60mL bottle contains 30 tablets and a 2 gram silica gel desiccant. Each bottle will be labelled as required per country requirement.	Refer to product label
Manufacturer	GSK	Refer to product label

6.2. Dose Modification

No dose adjustments are permitted in this study for DTG/3TC FDC or for CAR.

6.3. Method of Treatment Assignment

Informed consent must be obtained prior to any study procedures, including any screening assessment.

Participants will be assigned to study intervention in accordance with the computer-generated randomization schedule. The central randomization schedule will be generated by Pharmaceutical Product Development (PPD) using a validated SAS developed program.

Randomization and study intervention assignment will be facilitated by the interactive voice/web recognition system (IVRS/IWRS). Following confirmation of fulfilment of study entry criteria, study site personnel will be required to contact the IVRS/IWRS to register participants. Participants will be randomized in a 1:1 ratio to DTG/3TC FDC or the CAR arm, in accordance with the computer-generated randomization schedule. To control for treatment related factors that may impact study outcomes, randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). Each participant will be assigned a unique identifier (designating the participant's randomization code) and a unique treatment number which matches the randomized treatment assignment.

Participants who are randomly assigned into the trial and subsequently withdrawn may not be rescreened. Once a randomisation number has been assigned it must not be re-assigned.

6.4. Blinding

This is an open-label study; potential bias will be reduced by the following steps: central randomization. No summaries of the study data according to actual randomized treatment groups will be available to sponsor staff prior to the planned Week 24 preliminary analysis. Public presentation of the Week 24 analysis will not be done until after the last participant completes their last visit for the primary Week 48 analysis.

6.5. Preparation/Handling/Storage/Accountability

No special preparation of study intervention is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from ViiV/GSK.

- IP accountability will be evaluated using pill counts of unused DTG/3TC FDC only and not CAR. This assessment will be conducted each time the participant receives a new (refill) supply of DTG/3TC FDC through the Withdrawal visit or study completion. IP accountability records must be maintained throughout the course of the study. These data will be recorded in the participant's eCRF but will not be summarised for analysis purposes.

- Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic.

6.6. Treatment Compliance

When participants self-administer study interventions at home, compliance with DTG/3TC FDC or CAR will be assessed through querying the participant during the site visits and documented in the source documents and eCRF. A record of the number of DTG/3TC FDC tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for treatment delays will also be recorded in the case report form (eCRF) for both DTG/3TC FDC and CAR.

6.7. Concomitant Therapy

Refer to Appendix 6 for a full list of prohibited medications. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential DDIs between such treatments and the study interventions. The investigator should evaluate any potential DDIs at every visit, including reviewing the most current version of the U.S. or local prescribing information for DTG, 3TC and CAR, especially if any new concomitant medications are reported by participants. All concomitant medications (including oral contraception, implants or oral or topical hormone replacement therapy) taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

Concomitant medications (prescription and non-prescription) should be prescribed by the relevant health care provider/investigator and administered only as medically necessary during the Randomized and Continuation phases of the study (except prohibited medications described in Section 11.6). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

6.7.1. Permitted Medications and Non-Drug Therapies

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn and only

when scheduled visits are ≥4 weeks apart. This approach will minimize the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG/3TC FDC should be administered 2 hours before or 6 hours after taking antacid or laxative products containing polyvalent cations (e.g. aluminium and magnesium), sucralfate, or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable. Iron supplements can be taken with IP provided that all are taken together with a meal. Under fasted conditions, DTG +3TC should be given 2 hours prior to OR 6 hours after iron supplements.

Metformin concentrations may be increased by DTG. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control.

Clinical monitoring is recommended for participants taking methadone, as methadone maintenance therapy may need to be adjusted in some participants.

Non-protocol defined treatments or medical interventions (e.g., physical therapy, radiotherapy, surgical procedures) are permitted during the study for appropriate medical management of the participant.

6.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not ViiV is providing specific post-study treatment.

All participants on DTG/3TC FDC who successfully complete 52 weeks of treatment will have the opportunity to receive DTG/3TC FDC once daily in a Continuation Phase until:

- DTG and 3TC are each locally approved for use as part of a 2-drug regimen, and each of the single entities of DTG and 3TC are available to participants (e.g., through public health services or through their usual health insurance payer), or
- the actual DTG/3TC FDC tablet, if required by local regulations, is available, or
- the participant no longer derives clinical benefit, or
- the participant meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC 2-drug regimen is terminated.

The Continuation Phase is not applicable for participants in Sweden and Denmark.

The purpose of the Continuation Phase is to ensure provision of DTG/3TC FDC. Assessments during the Continuation Phase are limited and will include some safety laboratory assessments.

7. DISCONTINUATION CRITERIA

7.1. Discontinuation of Study Intervention

Participants permanently discontinuing study interventions are considered to be withdrawn from the study. Similarly, participants who enter the Continuation Phase but permanently discontinue participation in the Continuation Phase prior to transitioning to commercially available DTG + 3TC are considered to be withdrawn from study intervention and from the study. Withdrawn participants will not be replaced.

7.1.1. Virologic Criteria for Participant Management and Viral Resistance Testing

For the purposes of clinical management in this study, **suspected virologic withdrawal (SVW)** and **confirmed virologic withdrawal (CVW)** criteria are defined here, wherein the virologic withdrawal criteria are based on the HIV-1 RNA cut-off of 200 c/mL. Clinical management for **precautionary virologic withdrawal (PVW)** criteria are based on consecutive viral loads ≥50 and <200 c/mL.

Suspected Virologic Withdrawal criteria

- one assessment with HIV-1 RNA ≥ 200 c/mL after Day 1 with an immediately prior HIV-1 RNA <50 c/mL

Confirmed Virologic Withdrawal criteria

- one assessment with HIV-1 RNA ≥ 200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL

Precautionary Virologic Withdrawal criteria

- may be met after two consecutive assessments with HIV-1 RNA ≥50 and <200 c/mL without an identifiable, non-virologic cause (immunization, illness, non-adherence) and after discussion with Medical Monitor, OR
- will be met with three consecutive assessments with HIV-1 RNA ≥50 and <200 c/mL

7.1.1.1. Participants Meeting Virologic Management Criteria

Participants with HIV-1 RNA plasma levels ≥50 c/mL at any visit after Day 1 meet "virologic management" criterion and must have plasma HIV-1 RNA levels re-assessed using the algorithm shown in Figure 2. Plasma HIV-1 RNA values determined by the central laboratory only will be used to assess virologic management criteria. Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic. Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as meeting a "virologic management" criterion, the Investigator should query the participant regarding intercurrent illness, recent immunisation, or interruption of therapy.

All cases meeting "virologic management" criterion must be confirmed by a second measurement performed at least two weeks but not more than 4 weeks apart from

the date of the original sample, **unless** **delay is necessary to meet the requirements of confirmatory HIV-1 RNA testing as outlined below.**

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

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full doses of all study interventions.
- Confirmatory testing should be scheduled 4 weeks following any immunisation, during which time the participant should receive full doses of study interventions.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full doses of study interventions.
- The participant should have received full doses of study interventions for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done. Sites should contact the Medical Monitor to discuss individual participants, whenever necessary.

7.1.1.2. Managing Participants Meeting Precautionary Virologic Withdrawal (PVW) or Confirmed Virologic Withdrawal (CVW) Criteria

Once a participant has been confirmed as meeting PVW or CVW criteria, a 'plasma for storage' sample from the earliest viral load ≥200 c/mL [if such is available for a PVW case), or from the SVW visit [if ≥200 c/mL) for a CVW case] will be sent as soon as possible for genotypic and phenotypic resistance testing and the result made known to the Investigator if and when available. Plasma samples for storage also will be obtained at unscheduled visits including the time of CVW criteria (see Figure 2).

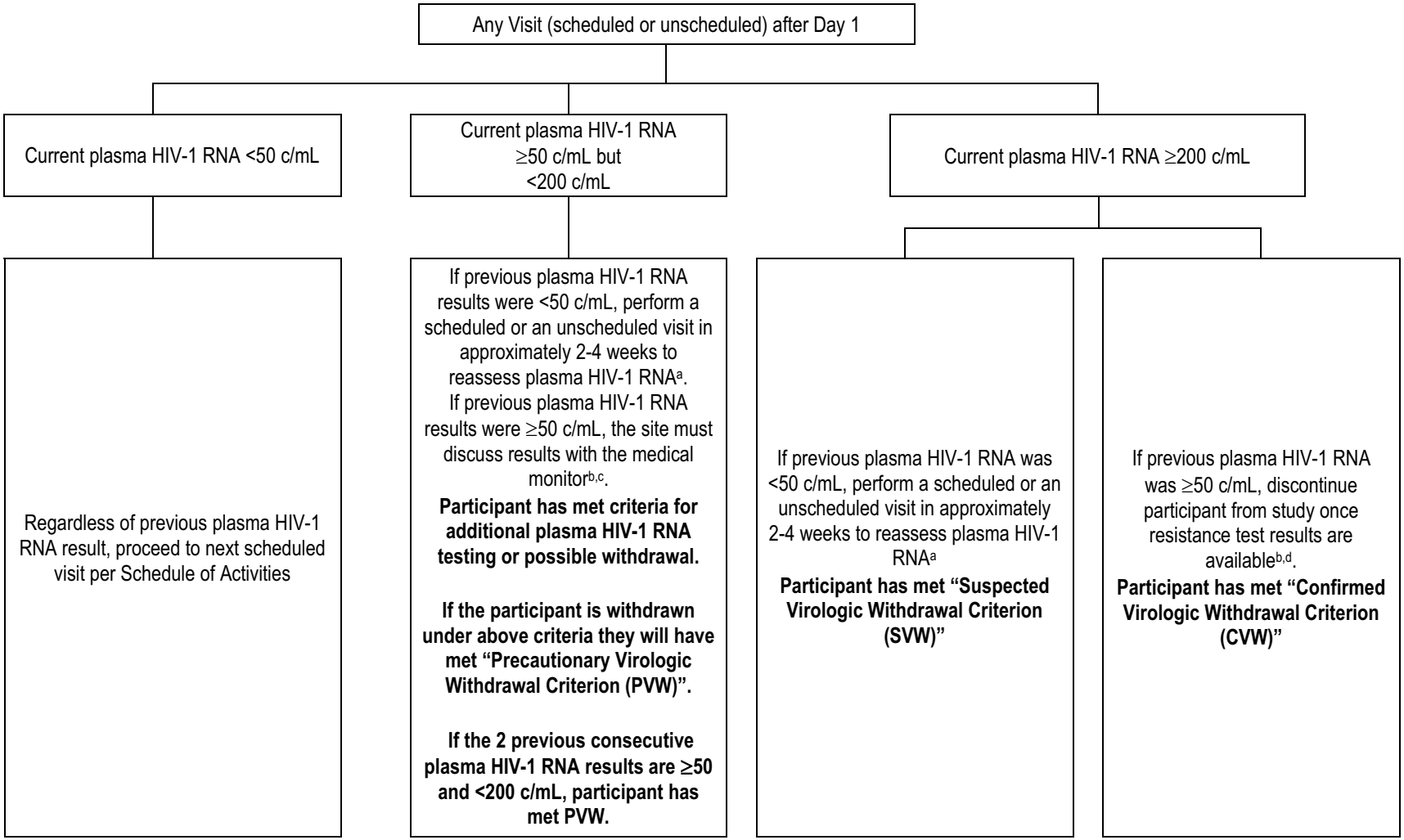
Participants may continue to receive study intervention at the discretion of the investigator until results of resistance testing are available at which time the participant must be discontinued from the study, except in cases where participant samples have HIV-1 RNA <500 c/mL, as noted below. **A participant who meets a PVW or CVW criterion must be discontinued from the study.** Selection of post-study ART regimen for participants meeting virologic withdrawal criteria will be recorded in the eCRF. To collect additional information on participants who meet CVW or PVW criteria, please see details on the Sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or PVW Criteria in Section 11.2.

The protease (PRO)/reverse transcriptase (RT)/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <500 c/mL. Nevertheless, for all participants who meet CVW criteria, plasma samples will be analysed in an attempt to obtain genotype/phenotype data on samples with HIV-1 RNA ≥200 c/mL, as possible. Participants with confirmed HIV-1 RNA levels between 200 c/mL and <500 c/mL should be transitioned off study intervention within 30 days even if no resistance testing data becomes available, as genotype/phenotype data may not be reliably generated from plasma samples collected from these participants. If the confirmed HIV-1 RNA level is ≥50 and <200 c/mL, and the decision is taken to withdraw the participant, resistance

testing will not be done and the participant should be transitioned off study intervention as soon as possible.

If a participant is prematurely discontinued from participation in the study, the Investigator must make every effort to perform the evaluations outlined in the Schedule of Activities. These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any participant from the study.

Figure 2 Criteria for Withdrawal or Re-Assessment of Plasma HIV-1 RNA



a. Investigators should not schedule reassessment blood draws in the presence of factors that could be associated with virologic blips, such as intercurrent infection, treatment interruption due to toxicity management or non-compliance, or vaccination. Participants should have received full doses of study intervention for at least 2 weeks at the time of plasma HIV-1 RNA reassessment.
b. In case of withdrawal, a sample from the initial visit where the HIV-1 RNA plasma level is ≥50 c/mL will be used for resistance testing only if HIV-1 RNA level is ≥200 c/mL. If resistance testing will not be done, withdrawing participants should be transitioned off study intervention as soon as possible.
c. The medical monitor and investigator should consider intercurrent illness, recent immunization, interruption of therapy or other non-virologic reasons associated with transient elevated HIV-1 RNA measurements ≥50 and <200 c/mL. If no non-virologic reasons are identified to explain the lack of virologic suppression, the participant must be withdrawn. If the Investigator and the medical monitor agree that the participant is experiencing a slow re-suppression due to one of the above issues, then a retest HIV-1 RNA measurement is required in approximately 2-4 weeks. If the HIV-1 RNA remains ≥50 c/mL on a second retest (the third consecutive HIV-1 RNA assessment), the participant must be withdrawn.
d. Participants with confirmed HIV-1 RNA results in the range ≥200 c/mL to <500 c/mL, should be transitioned off study intervention and withdrawn from study within 30 days regardless of whether resistance testing has been reported as genotype/phenotype data may not be reliably generated from plasma collected from these participants

7.1.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Section 11.9.1
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Liver Safety Required Actions and Follow up Assessments can be found in Section 11.9.

7.1.3. Temporary Discontinuation

Participants may have a temporary interruption to their study intervention for management of toxicities. Such interruption of study intervention does not require withdrawal from the study. However, consultation with the Medical Monitor is required.

7.1.4. Restart

If participant meets liver chemistry stopping criteria do not restart the participant with study intervention unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**,
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the participant.
- Refer to Section 11.9.2 for full guidance.

7.2. Withdrawal from the Study

Participants <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Participant or Investigator non-compliance;
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon;

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent;
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records;
- At the request of, GSK or ViiV Healthcare;
- The participant requires concurrent prohibited medications during the course of the study. The participant may remain in the study if in the opinion of the Investigator and the medical monitor, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the participant.

Participants must be discontinued from the study for any of the following reasons:

- Virologic withdrawal criteria as specified in Section 7.1.1 are met
- Participant is identified as having been mistakenly screened/randomized with exclusionary resistance (see Section 7.1.1)
- Participant requires substitution or dose modification of DTG, 3TC or any component of CAR. For participants on CAR, a switch from a PI boosted with ritonavir to the same PI boosted with cobicistat (and vice versa) and a switch from lamivudine to emtricitabine (and vice versa) is permitted per protocol.
- Liver toxicity where stopping criteria specified in Section 7.1.2 are met and no compelling alternate cause is identified
- Allergic reaction or Rash criteria as described in Section 11.3.1.5 and Section 11.3.1.6 are met and no compelling alternate cause is identified
- Renal toxicity as specified in Section 11.3.1.3 are met and no compelling alternate cause is identified
- Grade 4 clinical or laboratory AE considered causally related to study intervention
- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 8.2.6). As a reminder, females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

Refer to the Schedule of Activities (SoA) (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any participant from the study. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for participants with ongoing AEs, serious adverse events (SAEs) regardless

of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

Participants are not obligated to state the reason for withdrawal. However, a reason for withdrawal must be documented by the Investigator on the Completion/Withdrawal section of the electronic case report form (eCRF). Every effort should be made by the Investigator to follow-up participants who withdraw from the study.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 1.3).
- Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

Screening Assessments

Written informed consent must be obtained from each potentially eligible participant by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the IRB/Independent Ethics Committee (IEC). After signing an informed consent, participants will complete Screening assessments to determine participant eligibility. Each participant being screened for enrolment evaluation will be assigned a participant number at the Screening visit. This number will be given sequentially in chronological order of participant presentation according to a numeric roster provided by PPD.

Eligibility criteria must be assessed carefully at the Screening visit. Physical examinations should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Cardiovascular medical history/risk factors, including vital signs (as detailed in the eCRF) will be assessed at the Screening visit and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Background information to be collected at Screening includes demography (year of birth, sex, race and ethnicity), prior ART history, medical history and current medical conditions, menopause history, concomitant medications, assessment of CDC HIV-1 classification, a 12-lead ECG and laboratory assessments as detailed in Section 1.3.

Eligible participants may be randomly assigned immediately as soon as all Screening assessments are complete and the results are available and documented. All participants

will complete the Screening period up to 28 days prior to Baseline (Day 1) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. The Screening period of up to 28 days is to accommodate availability of all Screening assessment results, completion of source document verification to satisfy the Inclusion and Exclusion Criteria including the required previous HIV-1 RNA values, and scheduling. All Screening results **must** be available prior to randomization.

All information about the participant's current and any past regimen must be available for review by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/received during the 28-day screening period and under no circumstances may the participant be randomized in the absence of source documentation, even if there are delays in receipt of this information. A participant may be re-screened if the source documentation is obtained after the screening window closes.

Details regarding prior resistance data must be noted in the source documentation. Resistance testing reports with genotypic data **must** be provided to ViiV after screening and before randomization for review by ViiV. Sites must wait for the study virologists to confirm the lack of exclusionary resistance mutations, which will be provided to the site before the screening window closes. Details for tracking historic resistance report availability and sending to ViiV Virology for evaluation are described in the SRM. Details regarding baseline or prior resistance data must be noted in the source documentation. **If a participant is identified as having been mistakenly screened/randomized with exclusionary resistance, they will be withdrawn.**

Participants with chronic active hepatitis B virus infection are excluded. Evidence of Hepatitis B virus (HBV) infection is based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), and HBV DNA. HBV DNA testing will only be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).

All participants will be screened for syphilis at screening. Participants with untreated syphilis infection, defined as a positive Rapid Plasma Reagin (RPR) without clear documentation of treatment, are excluded unless they complete treatment during the 28-day screening window and 7 days prior to randomization. Participants who complete treatment after the screening window closes may be rescreened.

Participants who meet all entry criteria are randomized and assigned a randomization number. Participants not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new participant number one time unless they were excluded for reason of having exclusionary historic genotypic resistance or for a viral load ≥50c/mL at time of screening. Participants who are randomized into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

Baseline Assessments

At Day 1 and prior to randomization, any changes to the eligibility parameters must be assessed and any results required prior to randomization (e.g., Day 1 urine pregnancy test for women of childbearing potential) must be available and reviewed.

Other baseline information to be collected at Day 1 includes assessment of HIV risk factors and mode of transmission, general medical history and current medical conditions, and menopause history. Laboratory and health outcomes assessments will also be collected. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Refer to Section 1.3 for a summary of all procedures at the Baseline (Day 1) visit.

8.1. Efficacy Assessments

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Schedule of Activities (Section 1.3). Methods to be used may include but are not limited to the Abbott Realtime HIV-1 Assay lower limit of quantitation 40 c/mL. In some cases, (e.g., where the plasma HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ and CD8+ lymphocyte counts, CD4+/CD8+ ratio) according to the Schedule of Activities (Section 1.3).

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Schedule of Activities (Section 1.3). HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see Section 11.12). When assessing CDC stage at Screening/Baseline, consider only the latest available CD4 T-cell count, except when the participant had an active Stage 3 event in the 6 months prior to Screening. Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

CDC Stage 1, 2 or 3 at enrolment → Death.

8.1.1. Primary Efficacy Endpoint

The primary endpoint will be the proportion of participants with virologic failure endpoint as per FDA snapshot category at week 48 for the ITT-E population. Virologic

failure will include the following events; data in window not below 50 c/mL, discontinued for lack of efficacy, discontinued for other reason while not below 50 c/mL, and change in background therapy.

8.1.2. Secondary Efficacy Endpoints

- Proportion of participants with plasma HIV-1 RNA <50 c/mL at Weeks 24 and 48 using the Snapshot algorithm for the ITT-E population
- Percentage of participants with viral failure endpoint as per FDA snapshot category at Weeks 24
- Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell counts ratio at Weeks 24 and 48
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA) (Section 1.3).

8.2.1. Physical Examinations

Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g. in the current medical conditions or AE logs).

8.2.2. Vital Signs

- At the Screening visit, vital signs including height, weight and Body Mass Index (BMI) will be measured. The systolic and diastolic blood pressure will be measured in semi-supine position after 5 minutes rest. Body weight and BMI will also be assessed at each visit according to the Schedule of Activities (SoA) (Section 1.3).

8.2.3. Electrocardiograms

- A baseline 12-lead ECG will be conducted at the Screening visit, for possible use as a reference during the study (i.e. in evaluation of any pertinent cardiovascular event).

8.2.4. Clinical Safety Laboratory Assessments

Refer to Appendix 7 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. All protocol required laboratory assessments must be performed by central laboratory services, with the exception of exceptional circumstances during screening noted in Section 5. Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic. Laboratory assessments must be conducted in accordance with the Laboratory Manual, and SoA (Section 1.3). Laboratory requisition forms must be completed and samples

must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Q^2 Solutions and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by Q^2 Solutions.

- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification) the results must be recorded in the eCRF. Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic.
- Labs will be graded automatically by the central lab according to the DAIDS toxicity scales (See Section 11.11 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Section 11.7.

8.2.5. Suicidal Risk Monitoring

Participants with HIV infection occasionally may present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in people with a pre-existing history of depression or psychiatric illness) in some people being treated with INIs, including DTG. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the

investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicidality Severity Rating Scale (eC-SSRS). The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months); all subsequent questioning is in relation to the last assessment. The eC-SSRS is to be administered as a participant completed questionnaire specified in the SoA. The eC-SSRS will be conducted electronically by telephone or by computer/tablet connected to the internet.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to ViiV/GSK within 1 week of the investigator diagnosing a possible suicidality-related AE.

8.2.6. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and ending at the final Follow-up visit. If a pregnancy is reported, the investigator should inform ViiV/GSK/PPD within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 11.4.3.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the study intervention must be reported promptly to ViiV/GSK (or designee).

GSK's central safety department will forward this information to the ART Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of

ARV products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.

8.3. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 8.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 8. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 8.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 8.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 11.8.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 11.12) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to ViiV/GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 11.8), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

8.4. Treatment of Overdose

For this open-label study, any tablet intake exceeding the randomized daily number of tablets for DTG/3TC FDC will be considered an overdose [Dolutegravir (TIVICAY) Product Insert, 2017; EPIVIR Product Information, 2017]. ViiV Healthcare does not recommend specific treatment for an overdose of DTG/3TC FDC. As appropriate, the Investigator should use clinical judgment and also refer to the prescribing information for the individual drugs used for CAR in treating overdose in the CAR arm.

For the purposes of this study, an overdose is not an AE unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 11.8). If an overdose occurs and is associated with an adverse event requiring action, all study medications should be temporarily discontinued until the adverse event resolves.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until DTG/3TC FDC can no longer be detected systemically (at least 2 days).
- Obtain a plasma sample for PK analysis within 60 hours from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Liver Event

As part of the follow-up for any liver stopping event, a blood sample for PK analysis will be collected if it can be obtained within 60 hours of the last dose (See Section 11.9.1).

Overdose

Only if requested by the Medical Monitor, as part of the follow-up for any suspected overdose, a blood sample for PK analysis will be collected if it can be obtained within 60 hours from the date of the last dose of study intervention (See Section 8.4).

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Blood and urine are being collected to perform renal, bone and inflammatory biomarker assessments.

Renal biomarkers:

- Cystatin C (blood)
- Retinol Binding Protein (RBP, urine),
- Beta-2-Microglobulin (B2M, urine)
- Urine RBP/creatinine ratio
- Urine B2M/creatinine ratio
- urine albumin/creatinine ratio,
- urine protein/creatinine ratio,

- urine phosphate, and
- serum creatinine.

Bone biomarkers (blood):

- bone-specific alkaline phosphatase,
- procollagen type 1 N-propeptide,
- type 1 collagen cross-linked C-telopeptide,
- osteocalcin

Inflammatory Biomarkers (blood):

- Interleukin-6 (IL-6)
- High-sensitivity C reactive protein (hs-CRP)
- D-dimer
- Soluble CD14 (sCD14)
- Soluble CD163 (sCD163)

HbA1c and insulin and glucose for HOMA-IR calculation

Other Biomarkers:

- Whole blood will be used for measurement of telomere length.

Since the intention is to utilize these biomarkers for research purposes and the clinical significance of these results is uncertain, the Sponsor will not be reporting real time results of these assessments to the investigator except for Cystatin C (Day 1 only) and HbA1c.

8.9. Health Economics and Outcomes Research

Health outcomes assessments will be conducted according to the Schedule of Activities (SoA) (Section 1.3). In the event of translations being unavailable, no such assessments will be conducted and the responses will be considered as missing in the final analyses. Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments. Questionnaires will be administered on paper except the willingness to switch survey, which will be a verbal question.

The following health outcomes assessments will be utilized in this study:

- To assess the reason(s) for their participation and facilitate an understanding of participant's willingness to switch, participants will be asked a single item question prior to randomization.
- The HIV treatment satisfaction questionnaire (HIV TSQ) (status version) [Woodcock, 2001; Woodcock, 2006] is a 10-item self-reported scale that measures overall satisfaction with treatment and by specific domains e.g., convenience, flexibility.
- The Symptom Distress Module (also called the HIV Symptom Index or Symptoms Impact Questionnaire) is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment [Justice, 2001].

8.10. HIV-1 Polymerase Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide plasma for storage samples according to the Schedule of Activities (for potential viral genotypic and phenotypic analyses). Participants meeting CVW criteria will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting SVW criteria; these results will be reported to the investigator as soon as available to provide guidance for election of an alternative regimen

Details concerning the handling, labelling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for PRO, RT, and integrase assays.

A secondary endpoint of the study will be the incidence of observed genotypic and phenotypic resistance to DTG or 3TC and to CAR for participants meeting Virologic Withdrawal criteria. The virologic endpoint may also be assessed based on third-agent class.

8.10.1. HIV-1 Exploratory Analysis

HIV-1 exploratory analysis may be carried out for participants meeting virologic failure criteria, and for all participants to more broadly assess the contribution of Baseline genotypic information on study results. These tests may be carried out on whole blood or stored plasma samples collected at Baseline and/or on stored plasma samples from other relevant time points as long as this is feasible per local country and laboratory practices. These exploratory tests and analyses may include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, low level HIV-1 RNA quantitation, viral DNA quantitation and measurement of viral replicative capacity. HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from participants who have HIV-1 RNA ≥400 c/mL regardless of confirmatory HIV-1 RNA.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study is designed to show that the antiviral effect of switching to a simplified two-drug regimen of DTG/3TC FDC once-daily is not inferior to continuation of their CAR at week 48 in ART-experienced participants living with HIV-1.

Non-inferiority will be concluded if the upper bound of a two-sided 95% confidence interval for the difference in virologic failure rates between the two treatment arms is smaller than 5%. If r_d is the virologic failure rate on DTG/3TC FDC and r_f is the virologic failure rate on the CAR regimen, then the hypotheses can be written as follows:

$$H_0: \ r_d - r_f \geq 5\% \qquad H_1: r_d - r_f < 5\%$$

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

The original sample size calculation required approximately 300 participants per arm (from a target of 857 screened participants) based on a true virologic failure rate of 2.25% per arm, a non-inferiority margin of 4%, and a 2.5% one-sided significance level to provide approximately 91% power to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48.

The COVID-19 pandemic of 2019/2020 occurred during screening, and enrolment. Because of the COVID-19 pandemic, there is potential impact on participant compliance with study visits, study drug adherence, and data quality, and then consequently the virologic failure rate could be higher than originally expected. With the increase of assumed true virologic failure rate, we propose to change non-inferiority margin from 4% to 5%. Assuming a virologic failure rate of 3%, a non-inferiority margin of 5%, and a 2.5% one-sided significance level, a sample size of 245 participants per arm would provide approximately 90% power to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48. Based on the sample size recalculation and both statistical and practical considerations due to COVID-19 pandemic, a decision was made to terminate the study enrolment. At the time of enrolment termination, approximately 445 participants were randomized and 53 were in screening. Assuming a 20% screen failure rate the final number of participants is expected to be approximately 490 (245 per arm).

Rationale for non-inferiority margin

According to the FDA's 2015 guidance document (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015), the margin for switch trials is driven by the largest clinically tolerable virologic failure rate and could be from 4% to 6% depending on virologic failure rate. Per the FDA document, typical rates of virologic failure seen in switch studies range from 1 to 3 percent and a margin of 4%

for virologic failure rate was originally considered tolerable [CDER, 2015]. However due to the COVID-19 pandemic, the virologic failure rate could be higher than originally expected and hence the increase in the margin to 5%.

9.2.1.1. Response and virologic failure rate assumptions

Table 2 shows Snapshot response (HIV-1 RNA<50 c/mL) rates and Snapshot virologic failure (HIV-1 RNA ≥50 c/mL) rates in previous switch studies in ART-experienced participants living with HIV-1. Taken together and without considering the impact of the COVID-19 pandemic, these data suggest that a reasonable assumption for the true failure rate for the current ART control arm and the switch arm is 2.25%. Taking into consideration of the impact of COVID-19, we assume a virologic failure rate of 3% in both the CAR control arm and the switch arm.

Table 2 Snapshot Response and virologic failure rates in previous switch studies

Study	Treatment Arm	HIV-1 RNA <50 c/mL	Virologic Failure (HIV-1 RNA ≥50 c/mL)
Week 48			
SPIRIT[a,b]	RPV/FTC/TDF	89%	8/317 (2.5%)
STRATEGY-PI[c]	QUAD	94%	2/290 (<1%)
	PI + FTC/TDF	87%	2/139 (1%)
STRATEGY-NNRTI[d]	QUAD	93%	3/290 (1%)
	NNRTI + FTC/TDF	88%	1/143 (<1%)
SALT[e]	ATV/r+3TC	77%	Not available[f]
	ATV/r+2NRTIs	76%	Not available[f]
OLE[g]	LPV/r+3TC	88%	Not available[h]
	LPV/r+TDF/FTC or ABC/3TC	87%	Not available[h]
GS-292-0109[i]	E/C/F/TAF	97%	10/959 (1%)
	TDF-based regimen[j]	93%	6/477 (1%)
GS-US-311-1089[k]	TAF containing regimen	94%	1/333 (<1%)
	TDF regimen	93%	5/330 (2%)
SWORD1 & 2[l] (Overall)	DTG + RPV	95%	3/513(<1%)
	CAR	95%	6/511(1%)
SWORD1 & 2[l] (Female)	DTG + RPV	93%	1/120 (<1%)
	CAR	91%	3/108 (2.8%)
STRIIVING[m]	Early Switch DTG + ABC/3TC STR	80%	1/275 (<1%)
	Late Switch DTG + ABC/3TC STR	91%	3/244 (1%)
GS-US-380-1844[n]	BIC/TFC/TAF	94%	3/282(1.1%)
	ABC/DTG/3TC	95%	1/282(<1%)
GS-US-380-1878[o]	BIC/F/TAF	92%	5/290(1.7%)
	Current Regimen (Boosted ATV or DRV plus FTC/TDF or ABC/3TC)	89%	5/287(1.7%)
TANGO[p]	DTG/3TC	93%	1/369 (<1%)
	TAF-based regimen (TBR)	93%	2/372 (<1%)
Week 24			
STRIIVING[m]	DTG + ABC/3TC STR	85%	3/275 (1%)
	Current ART	88%	4/278 (1%)
BRAAVE2020[q]	BIC/F/TAF QD	96%	2/328 (<1%)
	Stay on baseline regimen (SBR)	95%	3/165 (2%)

E/C/F/TAF - elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide

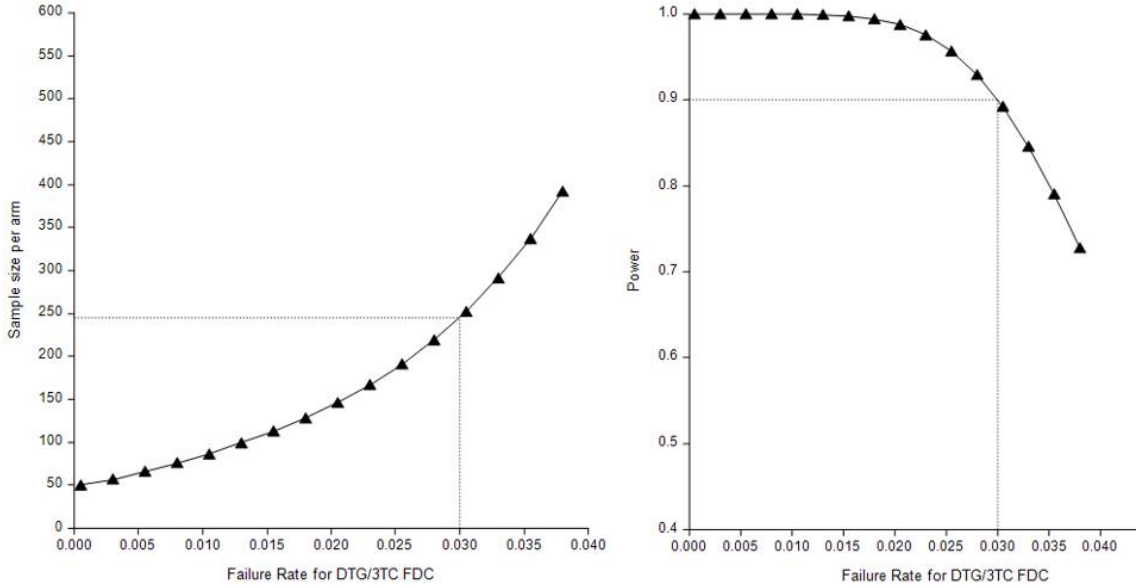
a. [Palella, 2014]
b. Participants in the PI/r +2 NRTIs arm were switched to RPV/FTC/TDF at Week 24; therefore Week 48 response data are not available for this treatment group.
c. [Arribas, 2014]
d. [Pozniak, 2014]
e. [Perez-Molina, 2015]
f. The percentage of snapshot virologic failure is not available; however, 4% in the 2-drug arm and 3% in the cART arm had protocol defined virologic failure (PDVF).
g. [Arribas, 2015]
h. The percentage of snapshot virologic failure is not available; however, 2% per arm had PDVF.
i. [Mills, 2016]
j. Elvitegravir (EVG)/Cobistat/TDF/FTC, EFV/TDF/FTC, ATV/Cobistat/TDF/FTC, or RTV/ATV/TDF/FTC
k. [Gallant, 2016]
l. [Llibre, 2017]

m. [Trottier, 2015]
n. [Molina, 2018]
o. [Daar, 2018]
p. [van Wyk, 2020]
q. [Hagins, 2020]

9.2.2. Sample Size Sensitivity

Figure 3 shows sensitivity of the required sample size to the true response rate for the DTG/3TC FDC arm assuming a 3% failure rate in the current ART non-switch arm and a 5% margin.

Figure 3 Sample size sensitivity for the Snapshot Virologic Failure



Power=90%, NI margin=5%, control arm failure rate=3%

N=245 per arm, NI margin=5%, control arm failure rate=3%

9.2.3. Sample Size Re-estimation or Adjustment

No further sample size re-estimation will be performed.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined (the analysis population for genotypic and phenotypic analyses will be fully described in the reporting and analysis plan [RAP]):

Population	Description
Intent-to-Treat Exposed	This population will consist of all randomized participants who receive at least one dose of study medication. Participants will be assessed according to their randomized treatment, regardless of the treatment they receive. Unless stated otherwise, the ITT-E Population will be used for efficacy analyses.

Population	Description
Per Protocol	This population will consist of participants in the ITT-E Population with the exception of protocol deviations which could affect the assessment of antiviral activity. The PP population will be used for sensitivity analyses of the primary efficacy measure. Further details will be described in the RAP.
Safety	The Safety Population is defined as all randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the treatment they actually received. Unless otherwise stated, the Safety Population will be used for safety analyses.

9.4. Statistical Analyses

Additionally, special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the main study RAP; alternatively, a separate RAP focusing on modified data handling rules (eg, changes to analysis populations, visit windows and endpoints) and analyses (eg, sensitivity analyses to assess impact of and account for missing data) may be prepared, taking in to account applicable regulatory guidance and industry best practices for handling such situations [FDA, 2020; EMA, 2020a; EMA, 2020b].

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	For the primary comparison, adjusted estimates of the difference in the virologic failure rate between the two arms will be presented along with CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. All CIs will be two-sided. For the statistical analysis, three strata (subgroups) will be formed according to the combinations of levels of the following categorical variables: • Baseline third agent: PI • Baseline third agent: INI • Baseline third agent: NNRTI The CMH estimate of the common difference in rates across strata will be calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two arms as follows: If nk is the number of DTG/3TC FDC treated participants, mk is the number of INI-, NNTRI-, or PI-based ART treated participants, and Nk = nk + mk is

Endpoint	Statistical Analysis Methods
	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 $\hat{d}_k$ are estimates of the differences in response rates between the two treatment arms, rd – rf, for the kth strata. The corresponding two-sided 95% CI will be calculated as $$\hat{d}_{cmh} \pm 1.96 \times \sqrt{\widehat{var}(\hat{d}_{cmh})}$$ using the variance estimator $\widehat{var}(\hat{d}_{cmh})$ given by [Sato, 1989], which is consistent in both sparse data and large strata. The full equation for this variance estimate is provided in the RAP. Full details will be contained in the RAP. The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either rd or rf are zero, and tests will be one-sided. Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported for each level of the categorical variable. Investigation of heterogeneity will be confined to the primary endpoint using the Week 48 Snapshot analysis. Tests of homogeneity will be assessed at the one-sided 10% level of significance. Further efficacy analyses to assess the sensitivity of the primary endpoint will be performed. Details of the sensitivity analyses will be included in the RAP and will include the responder endpoint as per FDA snapshot category, 'time to event' methods which censor participants who discontinue from the study with viral load <50 c/mL or for non-efficacy-treatment related reasons. In these analyses, participants will be considered to have had an event if they have a confirmed viral load ≥50 c/mL or discontinue for efficacy related reasons.

Endpoint	Statistical Analysis Methods
Secondary	Details for secondary efficacy endpoints including the Week 24 interim analysis will be discussed in the RAP. Resistance data will be summarized overall and by baseline third agent class. The incidence of HIV-1 disease progression (AIDS and death) will be presented. The proportion of participants with Snapshot virologic failure will be summarized by subgroups (e.g., age, race).
Exploratory	Full details will be described in the RAP

Data gathered after participants withdraw from IP will be listed but will not be included in summary tables. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window will be listed and will be included in the derivation of the Snapshot response at analysis visits of interest, but summary tables using OC datasets will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP. Any deviations from planned analyses will be detailed in the clinical study report.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	The observed case dataset will be the primary dataset used for analysis of safety endpoints. Exposure to study medication, measured by the number of weeks on study intervention, will be summarized by treatment group. The proportion of participants reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided: • Incidence and severity of all AEs • Incidence and severity of treatment related AEs • Incidence and severity of AEs leading to withdrawal • Incidence of SAEs The incidence and severity of treatment related AEs, SAEs and AEs leading to withdrawal will also be assessed by baseline third agent class and in those with creatinine clearance of between 30-49 mL/min/1.73m^2 compared to those with a creatinine clearance of $\geq$50 mL/min/1.73m^2.

	Further details will be detailed in the RAP. Laboratory and vital signs data will be summarized by visit and treatment group. In addition, the number and percentage of participants with graded laboratory toxicities (based on DAIDS categories) will be summarized by treatment group. The proportion of participants experiencing changes from Baseline in their National Cholesterol Education Program (NCEP) lipid categories will be summarized by treatment arm. Further details of safety analyses will be described in the RAP.
Exploratory	Full details will be described in the RAP

9.4.3. Other Analyses

Details of the analyses of Willingness to Switch and change from Baseline in HIV TSQ and SDM will be specified in the RAP.
The incidence of observed genotypic and phenotypic resistance to DTG, 3TC and other on-study ART will be summarized by treatment arm for participants meeting confirmed virologic withdrawal criteria. Details of the analyses to be performed will be specified in the RAP.

9.5. Interim Analyses

One analysis will be conducted to evaluate the primary objective of the protocol when all participants have completed their Week 48 visit. An interim analysis will be conducted when all participants have completed their Week 24 visit. To minimise bias, the Week 24 results will not be shared with participants and investigators, or presented externally until after the last participant completes their last visit for the primary Week 48 analysis.

Further data cuts and analyses may be conducted as necessary to support regulatory submissions and publications. The Week 48 analysis will be primary. No adjustment for multiplicity caused by repeated evaluation of the primary endpoint will be made as the Week 24 analyses will be secondary.

9.5.1. Independent Data Monitoring Committee (IDMC)

An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy in order to protect the ethical interests and well-being of participants and to protect the scientific validity of the study. An ad-hoc review of data by the IDMC will be triggered whenever the number of participants meeting CVW criteria in the DTG/3TC FDC arm exceeds thresholds pre-specified in the IDMC charter, to ensure that participants are not being sub-optimally treated. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

9.5.2. Analysis Datasets

The primary analysis set of data is based on virologic failure defined by the FDA snapshot algorithm. With the exception below, virologic failure includes participants who changed any component of background therapy to a new drug class, changed background components that were not permitted per protocol, or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48; participants who discontinued study intervention or study before Week 48 for lack or loss of efficacy and participants who are equal to or above 50 c/mL in the 48-week window.

A secondary analysis set of data is based on participants' responses at <50 c/mL calculated according to the FDA's snapshot algorithm. This algorithm treats all participants without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to visit window) as non-responders, as well as participants who switch their concomitant ART prior to the visit of interest, since no switches (with the exception below) are allowed in the protocol.

Note: A switch from a PI boosted with ritonavir to the same PI boosted with cobicistat (and vice versa) is permitted per protocol and a switch from lamivudine to emtricitabine and vice versa is also permitted and will not be considered as a change in background ART hence, will not incur a penalty in the Snapshot algorithm, regardless of reason or date of switch, as these agents are expected to have similar boosting effect and no impact on overall efficacy of the regimen.

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the visit of interest window (to be specified in the RAP). Full details of this snapshot algorithm will be contained in the RAP.

Another secondary set of data will treat participants as censored if they discontinue for reasons other than those related to treatment (AEs, tolerability and lack of efficacy). This data set will be the Treatment Related Discontinuation = Failure data set.

The observed case (OC) dataset, which uses only data that are available at a particular time point with no imputation for missing values, will be the primary dataset for assessing safety and will also be used for some analyses of efficacy and health outcomes. Further details will be provided in the RAP.

9.5.3. Treatment Comparisons

9.5.3.1. Primary Comparison of Interest

The primary analysis will be based on the ITT-E population using the Snapshot virologic failure dataset. The primary comparison will be made at a one-sided 2.5% level of significance. Treatment with DTG/3TC FDC will be declared non-inferior to the CAR if the upper bound of a two-sided 95% confidence interval for the difference between the two groups in virologic failure rates at Week 48 lies below 5%.

9.5.3.2. Other Comparisons of Interest

The analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population. If both analyses show non-inferiority, then the hypothesis that the antiviral effect of treatment with DTG/3TC FDC is superior to the CAR treatment will be tested using the same level of significance as for the tests of non-inferiority. Superiority will be declared if the upper bound of the confidence internal is below 0%.
The following key secondary comparison will be tested:

- Non-inferiority of switching to DTG/3TC FDC compared to continuation of CAR with respect to virologic success endpoint as per FDA snapshot category using a -12% non-inferiority margin.

No multiplicity adjustments for statistical testing of secondary endpoints will be performed; however, all tests will be pre-specified in the RAP.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B Core Antibody
ARV	Antiretroviral
ART	Antiretroviral therapy
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
c/mL	Copies/milliliter
CAR	Current ART regimen
cART	Combination ART
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
CMH	Cochran-Mantel Haenszel
CRF	Case Report Form
CI	Confidence interval
ConART	Concomitant ART therapy
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CV	Cardiovascular
CVW	Confirmed Virologic Withdrawal
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-Drug Interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DTG	Dolutegravir, TIVICAY
E/C/F/TAF	Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz

eGFR	Estimated glomerular filtration rate
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FTC	Emtricitabine
GCP	Good Clinical Practice
GCSP	GSK's Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GFR	Glomerular Filtration rate
HAART	Highly active ART therapy
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV TSQ	HIV treatment satisfaction questionnaire
HLA	Human leukocyte antigen
HOMA-IR	Homeostasis model of assessment – insulin resistance
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IVRS/IWRS	Interactive Voice/Web Recognition System
LDL	Low density lipoprotein
LPV	Lopinavir
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
m-ITT	Modified Intent to Treat

MRHD	maximum recommended human dose
MSDS	Material Safety Data Sheet
NADES	Non-Acquired Immuno-Deficiency Syndrome (AIDS)-Defining Events
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed Case
OCT-2	Organic cation transporter
PBMC	Peripheral Blood Mononuclear Cell
PDVF	Protocol defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per-protocol
PPD	Pharmaceutical Product Development
PSRAE	Possible suicidality-related adverse event
PVW	Precautionary virologic withdrawal
QTc	Corrected QT interval
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SDM	Symptom Distress Module
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TAF	Tenofovir alafenamide
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine, Truvada
TEN	Toxic epidermal necrolysis
TLOVR	Time To Loss Of Virologic Response
TSQ	Treatment Satisfaction Questionnaire
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell
WOCBP	Women of childbearing potential
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Trademark Information

Trademarks of the ViiV Healthcare group of companies
COMBIVIR
EPIVIR
EPZICOM/ KIVEXA
TIVICAY
TRIUMEQ
ZIAGEN

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Abbot Realtime HIV-1
Edurant
GenoSure
Genvoya
HIV TSQ
Monogram Biosciences
PhenoSense
SAS
SDM
Truvada

11.2. Appendix 2: A Sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or PVW Criteria

11.2.1. Rationale for CVW and PVW Sub-study

This sub-study will evaluate and determine the virologic response to subsequent regimens of participants who have virologic failure to DTG/3TC FDC. The evaluation period will start from the time the participant is discontinued from the 208090 study for confirmed virologic withdrawal (CVW) or precautionary virologic withdrawal (PVW) criteria while on DTG/3TC FDC, and will last for up to 12 months. The results of this study may provide information that will help guide treatment decisions for people living with HIV who virologically fail a DTG/3TC FDC regimen.

11.2.2. Sub-study Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To determine the drug regimens that are used after CVW or PVW with DTG/3TC FDC.	Incidence of drug regimens used as subsequent regimens after CVW or PVW with DTG/3TC FDC.
To determine the proportion of participants with CVW or PVW with DTG/3TC FDC who achieve virologic suppression with the subsequent regimen at the end of 12 months of follow up.	• Proportion with plasma HIV-1 RNA <50 copies/mL, 50-200 copies and >200 copies/mL through 12 months • Proportion with plasma HIV-1 RNA <50 copies/mL after switching to subsequent regimens
To describe the reasons for discontinuation of/switching from subsequent treatment regimen and reason for virologic failure	Describe reasons for switching from subsequent regimen and reasons for virologic failure

11.2.3. Sub-study Design

This is a prospective observational study that will enroll participants in 208090 who withdraw from the study for meeting CVW or PVW criteria. All participants who withdraw from the 208090 study for meeting CVW or PVW criteria while on DTG/3TC FDC and consent to participate will be followed for up to 12 months after withdrawal. The medical charts of participants who consent will be abstracted at baseline (time of withdrawal), 3, 6 and up to 12 months after withdrawal from the 208090 study. For participants who attend a separate clinic for HIV care after withdrawal from the 208090 study, the PI or designated site staff will be required to contact the clinic physician to collect the required information. The following information will be obtained:

- ART drug regimen(s) that participants started after withdrawal from the main study due to meeting CVW or PVW criteria
- Plasma HIV-1 RNA levels after regimen switch and up to 12 months after CVW or PVW date
- Reasons for virologic failure when the subsequent treatment regimen is changed nonadherence, tolerability, adverse event, etc.
- Reasons for switching when the subsequent treatment regimen is changed - virologic failure, tolerability, safety, adherence, convenience, etc.
- Adverse Events, SAEs or Death leading to ARV discontinuation
- Adverse Drug Reactions, SAEs or Death related to ViiV Healthcare products
- Pregnancy while on ViiV Healthcare products
- Concomitant Medications

Schedule of Activities

Procedures	**Baseline (after regimen switch upon withdrawal from 208090 main study)**	**3 months**	**6 months**	**12 months**
Written Informed Consent	X			
Current ART regimen	X	X	X	X
Plasma HIV-1 RNA (if available)	X	X	X	X
Reasons for Virologic Failure		X	X	X
Reasons for Switch (if subsequent regimen is changed)		X	X	X
Adverse Events, SAEs, or Death leading to ARV discontinuation	X	X	X	X
Adverse Drug Reactions, SAEs, or Death related to ViiV Healthcare products	X	X	X	X
Pregnancy while on ViiV Healthcare products[a]	X	X	X	X
Concomitant Medications	X	X	X	X

a. Investigator must collect pregnancy information on the appropriate form and submit to ViiV/GSK/PPD

Since this sub-study is an observational study of participants who have withdrawn from the main study, the protocol-specified withdrawal and stopping criteria are not applicable.

11.2.4. Sub-study data Collection

For this study, participant data will be entered into eCRFs, transmitted electronically to GSK or designee and supplemented with demographic and clinical data provided from the 208090 study in a validated data system.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.

Adverse events, SAEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.

eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of his or her site-specific data in the same format to maintain as the investigator copy. Participant initials will not be collected or transmitted to ViiV Healthcare/GSK according to ViiV Healthcare/GSK policy.

11.2.5. Statistical Considerations and Data Analysis

This is a descriptive study. No formal hypothesis will be tested. Where possible, frequency tables will be provided.

The endpoint assessing the proportion of participants with plasma HIV-1 RNA <50 copies/mL, 50-200 copies and >200 copies/mL at the end of 12 months will be based on an observed case analysis for this descriptive study.

Further details will be provided in the RAP.

11.3. Appendix 3: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (see Section 11.11). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 11.8.

Study intervention may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of study interventions will be allowed. Study interventions should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of study interventions or temporary interruption of one but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on participant management and study intervention interruptions based on the severity of the AE for specific toxicities. All changes in study intervention must be accurately recorded in the participant's eCRF.

Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study intervention at the discretion of the investigator. Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by study intervention, dosing may continue after discussion with the medical monitor.

Participants who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the interventions should have study intervention withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, study intervention may be restarted.

Should the same Grade 3 AE recur within 28 days in the same participant, study intervention should be permanently discontinued and the participant withdrawn from study. Participants experiencing Grade 3 AEs requiring permanent discontinuation of study intervention should be followed weekly until resolution of the AE and have withdrawal study evaluations completed. A Follow-up visit should be performed 4 weeks after the last dose of study interventions.

Participants with asymptomatic Grade 3 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue study intervention if the investigator has compelling evidence that the toxicity is not related to study intervention.

Exceptions are noted for lipid abnormalities in Section 11.3.1.7 and rash in Section 11.3.1.6.

Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have study intervention discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the study interventions, dosing may continue after discussion with and assent from the medical monitor. Participants should be rechecked each week until the AE returns to Grade 2.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study intervention should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above.

Participants with asymptomatic Grade 4 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to study intervention. Exceptions are noted for lipid abnormalities in Section 11.3.1.7. An in-clinic Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

11.3.1. Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to study intervention are provided below.

Participants who permanently discontinue study intervention for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations (see Section 7.2).

11.3.1.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology during administration of study intervention and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 11.9.1.

11.3.1.2. Restarting Study Intervention

Refer to Section 11.9.2 for details on drug restart following transient resolving liver events not related to study intervention.

11.3.1.3. Decline in Renal Function

Participants who experience an increase in serum creatinine from Baseline of 45 micromoles/liter (μMol/L) (or 0.5 milligrams/deciliter [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis, urine albumin/creatinine and urine total protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Participants who experience progression to an estimated GFR (using the CKD-EPI-creatinine) of <30 mL/min/1.73m^2 must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis, urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should be done at this confirmatory visit. If an estimated GFR of <30 mL/min/1.73m^2 is confirmed using the CKD-EPI (cystatin C), then study intervention should be discontinued and the participant withdrawn from the study (as dose adjustment is needed for NRTIs, which is not possible in a study of a fixed-dose combination tablet).

11.3.1.4. Proteinuria

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine albumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study medical monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 μmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study medical monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and medical monitor.

11.3.1.5. Allergic reaction

Participants may continue study intervention for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study intervention should permanently discontinue study intervention and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE.

11.3.1.6. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB and any IB supplements [GlaxoSmithKline Document Number RM2007/00683/11, GlaxoSmithKline Document Number 2017N352880_00, GlaxoSmithKline Document Number 2017N352880_01].

Participants with an isolated Grade 1 rash may continue study intervention at the Investigator's discretion. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Participants may continue study intervention for an isolated Grade 2 rash. However, study intervention (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The participant should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Participants should permanently discontinue study intervention [and all other concurrent medication(s) suspected in the Investigators causality assessment] for an isolated Grade 3 or 4 rash, except where the aetiology of the rash has been definitively diagnosed as NOT attributable to study intervention (see below), and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g., viral infection) or start of concomitant medication.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings, Section 11.10.

However, if the aetiology of the rash has been definitively diagnosed as being unrelated to study intervention and due to a specific medical event or a concomitant infection or a concomitant non-study medication, routine management should be performed and

documentation of the diagnosis provided. In this situation, the study intervention should be continued.

11.3.1.7. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Schedule of Activities (Section 1.3). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study intervention.

REFERENCE:

Inker LA, Schmid CH, Tighiouart H, et al; Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med*. 2012;367:20-9.

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009;150:604-12.

11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

11.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

11.4.2. Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 3.

The list does not apply to FRP with same sex partners or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent

basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Table 3 List of Highly Effective Contraceptive Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

11.4.3. Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to ViiV/GSK/PPD within 2 weeks of learning of a participant's pregnancy.
- Participants will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to ViiV/GSK/PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers and licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to ViiV/GSK/PPD as described in Appendix 8. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

11.5. Appendix 5: Child-Pugh Classification

A participant is classified with mild hepatic impairment (Class CCI) if their overall sum of scores is CCI points, moderate hepatic impairment (Class CCI) if their overall sum of scores is CCI points, and severe hepatic impairment (Class CCI) if their overall sum of scores is CCI based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 4). For participants requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 4 Child-Pugh System

Finding	Points Scored for Each Observed Finding
	CCI
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

[Pugh, 1973; Lucey, 1997]

References

Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg*. 1997;3:628-37.

Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-49.

11.6. Appendix 6: Prohibited Medications

The following 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.
- For participants with an **unanticipated** requirement for HCV therapy during study, interferon or any other medications that have a potential for adverse drug-drug interactions with study intervention are prohibited during the conduct of the study.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis [James, 2009].

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine
- St. John's wort (*Hypericum perforatum*)

Dofetilide, pilsicainide and fampridine are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide, pilsicainide or fampridine concentrations and potential for toxicity.

Any substrate of organic cation transporter 2 (OCT2), with a narrow therapeutic window should not be administered concurrently with DTG containing products.

Note: Any prohibited medication should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the CAR regimen, please consult the local prescribing information.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

11.7. Appendix 7: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by central laboratory services, with the exception of exceptional circumstances during screening noted in Section 5. Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol Required Safety Laboratory Assessments

Hematology:			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
MCH			
Clinical Chemistry:			
BUN	Potassium	AST	Total bilirubin[a] Direct bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[b]	Total CO2	Alkaline phosphatase	GFR/Creatinine clearance[c]
Sodium		Phosphate	Cystatin-C (Day 1 only)
Calcium		Protein	Creatine Phosphokinase
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Urinalysis			
specific gravity, pH, glucose, protein, blood and ketones by dipstick (with microscopic examination if blood or protein is abnormal), urine albumin/creatinine ratio, urine protein/creatinine ratio, urine phosphate			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ and CD8+ lymphocyte counts, CD4+/CD8+ cell count ratio			
Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA)			
Hepatitis C (anti-HCV)			
PT/INR			
Pregnancy test for women of childbearing potential[f]			
Renal biomarkers including Cystatin-C (blood), Retinol Binding Protein (RBP, urine); and Beta-2-Microglobulin (B2M, urine), urine RBP/creatinine ratio, urine B2M/creatinine ratio[g]			
Bone biomarkers including: Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin			
Inflammation Biomarkers: Interleukin-6 (IL-6), High-sensitivity C reactive protein (hs-CRP), D-dimer, Soluble CD14 (sCD14), Soluble CD163 (sCD163)			
HbA1c and insulin and glucose for HOMA-IR calculation			

MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO_2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HbsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio, HbA1c = glycated haemoglobin, HOMA-IR = homeostasis model of assessment – insulin resistance, IL-6 = interleukin-6, hs-CRP = high-sensitivity C reactive protein, sCD = soluble CD.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
c) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-creatinine) [Levey, 2009]. In addition, GFR will be estimated by the central laboratory using the CKD-EPI-cystatin C [Inker, 2012] at day 1 and when indicated by renal toxicity criteria.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f) Urine pregnancy test/ serum pregnancy test will be performed according to the Schedule of Activities.
g) The intention is to utilize these biomarker data for research purposes; the sponsor will not be reporting real-time results of these assessments to the investigator, except for Cystatin C (Day 1 only) and HbA1c.

References

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009;150:604-12.

11.8. Appendix 8: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.8.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.8.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from

baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

11.8.4. Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to ViiV/GSK/PPD in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by ViiV/GSK/PPD. In this case, all participant identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to ViiV/GSK/PPD.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the categories in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Section 11.10:

- Grade 1/ Mild
- Grade 2/ Moderate
- Grade 3/ Severe
- Grade 4/ Potentially life threatening
- Grade 5/ Death

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to ViiV/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ViiV/GSK/PPD.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV/GSK/PPD to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide ViiV/GSK with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to ViiV/GSK/PPD within 24 hours of receipt of the information.

11.8.5. Reporting of SAE and other events to ViiV/GSK/PPD

Reporting of SAEs and other events to ViiV/GSK/PPD

- The primary mechanism for reporting SAE to ViiV/GSK/PPD will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the SRM

SAE Reporting to GSK via Paper CRF

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and scan and email it to the Medical Monitor
- Contacts for SAE reporting can be found in the SRM

11.9. Appendix 9: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart Guidelines

Study treatment refers to all drugs evaluated in the study and therefore includes ViiV study intervention and non-ViiV ART therapies that can be used in combination with ViiV products or other ART interventions.

A liver stopping event is an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that trigger discontinuation of study treatment and requirement of additional actions and follow up assessments to be performed.

A liver monitoring event is as an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that triggers increased monitoring of the participant's liver chemistries, but no action is taken with study treatment unless liver chemistry stopping criteria are met.

11.9.1. Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If baseline ALT ≤1.5x ULN	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If baseline ALT >1.5x ULN	
ALT-absolute	ALT ≥5x baseline OR >500 U/L (whichever occurs first)
ALT Increase	ALT ≥3x baseline but <5x baseline persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3x baseline OR >300 U/L (whichever occurs first) **and** bilirubin ≥2xULN
Cannot Monitor	ALT ≥3x baseline but <5x baseline and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3x baseline and symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**

• Immediately discontinue study intervention.
• Report the event to the Medical Monitor **within 24 hours**.
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]**.**
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
• Perform liver event follow up assessments.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).
• **Do not restart** participant with study intervention unless allowed per protocol and VSLC approval **is granted** (refer to Section 11.9.2).
• If restart is **not allowed or not granted**, permanently discontinue study intervention and may continue participant in the study for any protocol specified follow up assessments.
 	
MONITORING:
• Make every reasonable attempt to have participants return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments.
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline.
• A specialist or hepatology consultation is recommended.
	Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below:
	• Viral hepatitis serology, including:
	  • Hepatitis A immunoglobulin M (IgM) antibody;
	  • HBsAg and hepatitis B core antibody;
	  • Hepatitis C RNA;
	  • Hepatitis E IgM antibody.
	• Cytomegalovirus IgM antibody.
	• Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
	• Syphilis screening.
	• Drugs of abuse screen, including alcohol.
	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must contact the Medical Monitor when this test is required.
	• Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4].
	• Serum CPK and lactate dehydrogenase (LDH).
	• Gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin
	• International normalized ratio (INR)
	• Fractionate bilirubin, if total bilirubin ≥1.5xULN.
	• Obtain complete blood count with

	differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy eCRF forms. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake eCRF.

CPK - creatine phosphokinase

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
If baseline ALT ≤1.5x ULN, ALT ≥5x ULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, monitor participant every 2 weeks until resolution to ALT <5x ULN.	• Notify the Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return every 1 – 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5×ULN on 2 consecutive evaluations) • If at any time participant meets the liver chemistry stopping criteria, proceed as described above
If baseline ALT >1.5x ULN, ALT ≥3x baseline and <5x baseline and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, monitor participant every 2 weeks until resolution to ALT <3x baseline	

Reference

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

11.9.2. Study Intervention Restart after Stopping for Liver Criteria

If a participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant

If VSLC approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

In Phase III, **drug restart** may be considered for liver events with a clear underlying cause (e.g., biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis or hypersensitivity, and drug not

associated with human leukocyte antigen (HLA) marker of liver injury, when liver chemistries improve to within 1.5x baseline and ALT<3xULN) (Table 6, Figure 4).

Drug Restart

Phase III "drug restart" can be approved by the VSLC for **transient, defined non-drug-induced liver injury if no evidence of:**

- immunoallergic injury /HLA association with injury
- drug-induced liver injury (DILI)
- alcoholic hepatitis

Study intervention is held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 4):

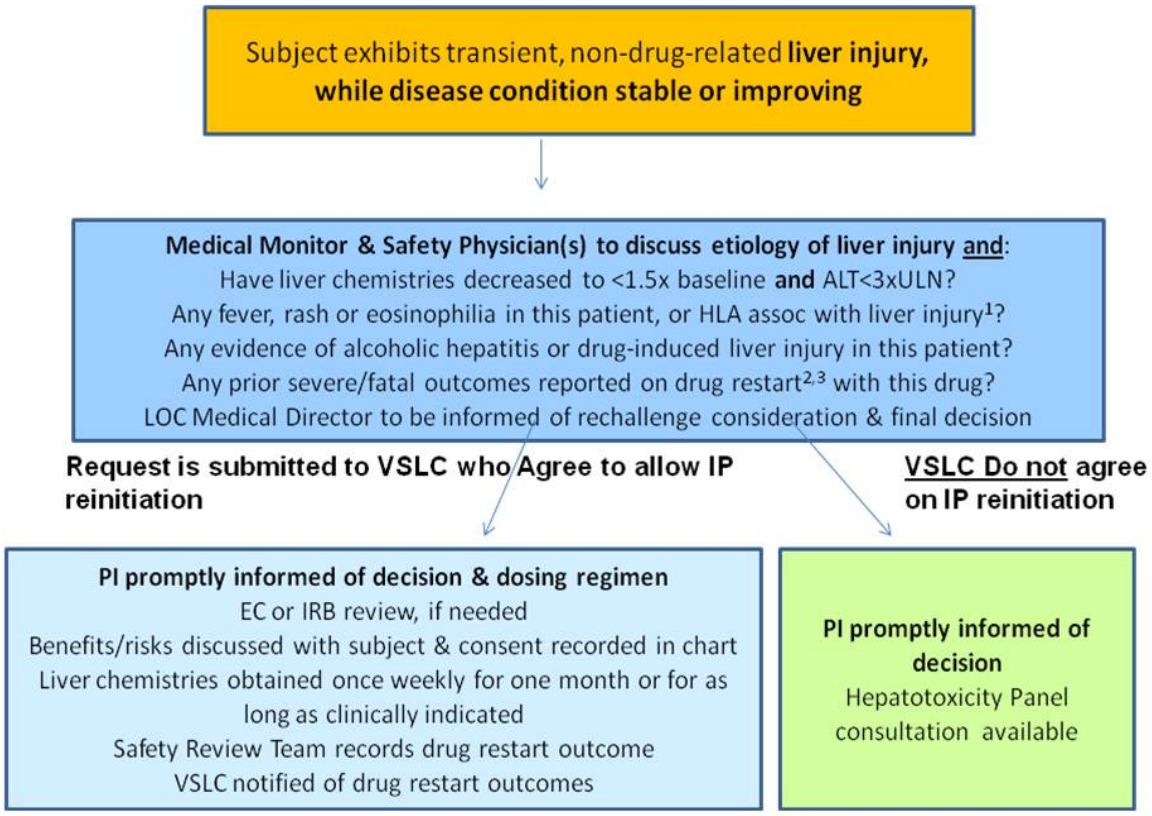
- PI requests consideration of drug re-initiation for a participant stable or improving on study intervention, who exhibits liver chemistry elevation meeting participant stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
  - In setting of a definitive non-study-drug-related diagnosis (e.g., acute viral or syphilitic hepatitis), restart will be considered once ALT <3x ULN (for participants with baseline ALT <1.5x ULN) or < 3x baseline ALT value (for participants with baseline ALT >1.5x ULN).
- Medical monitor and Clinical Safety Physician to review the participant's diagnosis, restart risk factors and complete checklist (Table 6).
  - The LOC medical director (ViiV Healthcare and GSK where applicable) should be informed that study intervention restart is under consideration and of the final decision, whether or not to proceed.

Table 6 Checklist for Phase III drug restart after well-explained liver injury (e.g., biliary, pancreatic, hypotensive events, congestive heart failure, acute viral hepatitis), improving to liver chem.≤1.5x baseline & ALT<3xULN

	Yes	No
Was participant stable or improving on study intervention?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• study intervention has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate)		
Previous drug history		

- Relevant physicians must review and agree on request for drug restart:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader.
- Hepatotoxicity Panel consultation is available.
- Justification for drug restart outlining the benefit and risk for this participant must be recorded by GSK's Global Clinical Safety and Pharmacovigilance (GCSP) Physician and sent to the VSLC Secretary.
  - VSLC must approve drug re-initiation and dosing regimen

Figure 4 VSLC process for drug restart approval or disapproval



1. 1. Andrade, 2009; 2. Papay, 2009; 3. Hunt, 2010

Medical Monitor, GCSP Physician and PI actions for Restart following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's restart decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.

- The Safety Review Team must record restart outcomes and the GCSP Physician must send these to the VSLC
    - All severe reactions (restart associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug restart must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug restart, as required.
- If drug re-initiation VSLC-approved, the participant must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- The participant's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***once weekly for 'restart' cases*** for one month or for as long as clinically indicated following drug re-initiation. If participant exhibits protocol-defined liver chemistry elevations, study intervention should be discontinued as protocol specified.

VSLC and the IRB/IEC must be informed of the participant's outcome following drug restart.

Restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting participant stopping criteria
- 2 = recurrent liver chemistry elevation meeting participant stopping criteria
- 3 = serious adverse event
- 4 = fatality

References

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009; 8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010; 52:2216-2222.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

11.10. Appendix 10: Regulatory, Ethical and Study Oversight Considerations

11.10.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

11.10.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.10.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

11.10.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.10.5. Committees Structure

Full details of the methods, timing, decision criteria and operating characteristics of the Independent Data Monitoring Committee (IDMC) will be pre-specified in the IDMC Charter.

11.10.6. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.10.7. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV/GSK site or other mutually-agreeable location.
- ViiV/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with ViiV/GSK Policy.

11.10.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.10.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM.

11.10.10. Study and Site Closure

ViiV/GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of ViiV/GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

11.11. Appendix 11: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

VERSION 2.1, March 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as **grade 5**

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

Major Clinical Conditions Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile +5mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23 in source DAIDS Table).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENIN
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENIN
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENIN
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech- language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan- uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENIN G
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness 10	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
2 to 5 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for- height z-score < -2 to -3	WHO Weight-for- height z-score < -3	WHO Weight-for-height z-score < -3 with life- threatening consequences
< 2 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for- length z-score < -2 to -3	WHO Weight-for- length z-score < -3	WHO Weight-for-length z-score < -3 with life- threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23 in source DAIDS Table).

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs:
http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and
http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN with other signs and symptoms of hepatotoxicity.	≥ 5.0 x ULN with life-threatening consequences (e.g., signs and symptoms of liver failure).
≤ 28 days of age	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life- threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

eGFR - estimated glomerular filtration rate

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *< 0.600 x* 10^9 to < 0.650 x 10^9	500 to < 600 *0.500 x* 10^{9_9} *to* *< 0.600 x* 10^9	350 to < 500 *0350 x* 10^9 *to* *< 0.500 x* 10^9	< 350 *< 0.350 x* 10^9
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x* 10^9 *to 1.000 x* 10^9	600 to 799 *0.600 x* 10^9 *to 0.799 x* 10^9	400 to 599 *0.400 x* 10^9 *to 0.599 x* 10^9	< 400 *< 0.400 x* 10^9
2 to 7 days of age	1,250 to 1,500 *1.250 x* 10^9 *to 1.500 x* 10^9	1,000 to 1,249 *1.000 x* 10^9 *to 1.249 x* 10^9	750 to 999 *0.750 x* 10^9 *to 0.999 x* 10^9	< 750 *< 0.750 x* 10^9
≤ 1 day of age	4,000 to 5,000 *4.000 x* 10^9 *to 5.000 x* 10^9	3,000 to 3,999 *3.000 x* 10^9 *to 3.999 x* 10^9	1,500 to 2,999 *1.500 x* 10^9 *to 2.999 x* 10^9	< 1,500 *< 1.500 x* 10^9
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥ 13 years of age who have been on hormone therapy for more than 6 consecutive months grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the femaile sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A: Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], **High** (mg/dL; *µmol/L*)[19] ***Term Neonate***[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. Mar 2017. Available from: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf (date accessed: 24 Jan 2018).

11.12. Appendix 12: CDC Classification for HIV-1 Infection (2014)

- Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.
- **HIV infection, stage 0**
- Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.
- **HIV infection, stage 1**
- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.
- **HIV infection, stage 2**
- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.
- **HIV infection, stage 3 (AIDS)**
- Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).
- Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.
- **HIV infection, stage unknown**
- Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.
- **Stage-3-defining opportunistic illnesses in HIV infection**
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary

- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

11.13. Appendix 13: Country-specific requirements

United Kingdom

This requirement has been included based on requests from the Medicines and Healthcare products Regulatory Agency (MHRA) to include information on the specific duration of the Continuation Phase/Study Intervention for similar Phase III trials being conducted with dolutegravir.

Study Duration

In this study, the date of last study intervention administration in the UK will be determined by the completion of the 52 week randomized phase of the study for the last UK participant enrolled (it will not be determined by the completion of the Continuation Phase). The last participant will be enrolled by Q1 2020/Q2 2020, and hence the last study intervention administration will occur by Q1 2021/Q2 2021. (Note: The Continuation Phase is intended to provide participants receiving DTG/3TC FDC with post-study access to DTG/3TC FDC until DTG plus 3TC is approved as a 2-drug regimen in their local countries. For participants in the UK, the Continuation Phase is not anticipated to be required as the 2-drug regimen of DTG/3TC FDC is anticipated to be approved by Q3/Q4 2020.

Sweden and Denmark

A country specific protocol amendment, 208090 Amendment 03/SWE-DEN-1, was previously published on 29-July-2019 for Sweden and Denmark to remove all references to the Continuation Phase. Participants in Sweden and Denmark in both treatment arms will finish the study at Week 52. This amendment was a regulatory requirement for Sweden and Denmark to update the protocol with a clear time for the study´s conclusion based on scientific basis without any reference to market approval. Protocol text in the current global protocol amendment 04 related to the continuation phase does not apply to Sweden and Denmark. A summary of sections that reference the continuation phase is included here:

- Section 1: Protocol Summary, Section 1.2: Study Schematic,
- Section 1.3: Schedule of Activities and footnotes
- Section 2.3.1: Risk Assessment,
- Section 3: Objectives and Endpoints
- Section 4.1: Overall Design
- Section 4.3: Participant and Study Completion
- Section 6.7: Concomitant Therapy
- Section 6.8: Treatment after the end of the study
- Section 7.1: Discontinuation of study intervention

China

A country specific protocol amendment, 208090 Amendment 03/CHI-1, was previously published on 31-May-2019 for China based on a requirement to perform all laboratory

analysis in-country and the unavailability of laboratory support in-country to conduct all of the protocol required analyses. Updates from global protocol amendment 04 will be incorporated into a country specific amendment for China, 208090 Amendment 04/CHI-1.

11.14. Appendix 14: COVID-19 Pandemic and Clinical Trial Continuity

Background

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participant's ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to ensure that there are no gaps in HIV-1 treatment for participants enrolled in this clinical study, through continuous access to antiretroviral therapy.

In order to maintain the scientific integrity of the study, and adhere to updated guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate against any impact of COVID-19 are well documented in the trial database.

A "Memo to Dolutegravir Clinical Trial Investigators and Study Staff" was issued on March 25th, 2020 and served as a record of approved emergency actions being taken within this clinical trial to manage issues related to COVID-19. That memo continues to serve as record of approved actions which can be fully implemented by Investigators, in advance of this protocol guidance. This appendix will remain consistent with the guidance provided within the March 25, 2020 "Memo to Dolutegravir Clinical Trial Investigators and Study Staff" and will also serve to provide additional protocol documentation requirements and procedures.

This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary.

This appendix **does not** apply to participant management issues that are unrelated to a specific, and documented, impact from COVID-19.

11.14.1. Changes to Study Visits and Study Procedures

- When site staff resources are limited due to COVID-19, abbreviated study visits may proceed without conducting all protocol-specified additional assessments (e.g. lab tests, questionnaires, etc.). If laboratory testing will be missed for more than one consecutive visit, medical monitor pre-notification is required, and all efforts should be made to find alternative approaches for lab testing.
- Consider alternative travel options for participants, if possible.

- When central laboratory testing is not possible at a particular visit, tests for management of participant safety, including HIV-1 RNA may be performed at an appropriately authorised/accredited local laboratory (or other relevant clinical facility), if this can be done within local restrictions on physical distancing. The site should proactively inform PPD/the sponsor about such instances. Local laboratory results done as per routine follow-up, including HIV-1 RNA, may be used to inform safety and patient management decisions. Results should be retained in source records and added to the eCRF.
    - If labs are collected on site and cannot be processed (either via central lab shipping, or local labs), freeze (and maintain at correct temperature for later processing) those samples that are sent frozen. Please safely discard ambient samples per site standards.
- When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including AEs/SAEs, from the participant through alternative means, e.g. by telephone contact. The assessment should include inquiries to determine if the participant has been impacted by COVID-19. Other protocol assessments and procedures as specified in the Schedule of Activities should be completed where possible (e.g. answer questions, update concomitant medications, emphasize adherence, plan/schedule participants return for next scheduled visit). This information should be placed in source records and entered into the eCRF when next possible. If the eC-SSRS assessment is able to be completed as part of the remote telephone visit, participants can complete the eC-SSRS at home by providing them with the activation code and the phone number or URL. Where possible, the site should be in contact with the participant before and after the completion of the assessment to ensure proper follow-up of positive alerts and have plans in place for addressing any positive results, and referring for care as necessary. The HIV TSQ and SDM questionnaires may be completed over the phone.
- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

11.14.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as

the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

Any updated informed consent form or other participant-facing materials should be provided to participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

The changes to the protocol, including COVID-19 related changes may be implemented before an ICF including COVID-19 related updates will be signed.

11.14.3. Direct-To-Patient (DTP) Shipment of Study IP

If a participant is unable to attend a study visit or to come to the site to pick-up investigational product (IP) due to site restrictions, or due to an inability to travel to the site (for personal precaution/sequestration, or government mandated travel restrictions, etc.), sites can consider DTP shipments of drug, from the site, to the participant, to ensure access to medicines. All other options, including alternative travel options for participants, should be considered before reverting to DTP shipments.

- If the study site is considering DTP shipment of IP, the site must first verify if DTP IP dispensing by investigators/hospital pharmacies is locally permitted and **whether it requires regulatory and/or local ethics pre-approval, or post-hoc notification.**
- The study participant should express his/her agreement for DTP shipment and the sharing of their personal information with any third-party couriers (as applicable), in accordance with local requirements. This agreement should be documented in source records.
- Enough IP to bridge to the next scheduled study visit can be supplied. For example, if the next visit is 12 weeks away, a 12-week supply can be dispensed via the IRT system

  NOTE: When the visit interval is only 4 weeks, then at least 8 weeks of IP can be provided to the participant
- Ensure local courier vendors, or vendors of hospital pharmacies, can ensure proper in-transit temperature monitoring, have enough shipper boxes and temperature loggers and can document storage conditions during IP transportation.
- Where temperature monitoring is not available, oral DTG/3TC FDC can be shipped at ambient temperatures with couriers that can provide shipper boxes capable of maintaining the shipment temperature storage requirements as described in the study guides. The risk of going outside of the excursion ranges

listed in the study guide should be evaluated and documented. Proper documentation of the shipment should be maintained. In all cases IP accountability must be maintained, and all DTP dispensing documentation should be reflected in source records and dispensing logs per GCP.

- Please refer to your CRA or local study manager for support with the DTP process, ensuring reference to current sponsor guidance and arrangement of a courier that can support shipment of IP directly to participants.
- Remember that any courier deliveries can be affected by limitations of movements imposed by governments in relation to COVID-19.
- Local courier vendors should be equipped to reduce risks of COVID-19 contamination during transportation.

11.14.4. COVID-19 Experimental Agents

If any treatments for COVID-19 are planned for a study participant, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

If any participants are being considered for enrolment into clinical studies for COVID-19 treatment or vaccinations, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate. The protocols do not allow for enrolment in other interventional studies, though, there may be exceptions in this pandemic. Please discuss with the study team and Medical monitor.

11.14.5. COVID-19 Specific Data Capture

11.14.5.1. Capturing COVID-19 Specific Protocol Deviations

In order to summarise the impact of COVID-19 in a systematic way and in line with regulatory authorities' recommendations, any study-level impact around COVID-19 will be documented as a protocol deviation. This will include the permissible actions summarized in this Appendix, which are taken to protect patient safety, including DTP supply of IP and remote study visits as well as missed visits and assessments as a result of logistical challenges resulting from COVID-19.

Although the conduct of remote visits and the continuity of antiretroviral therapy, via DTP supply of IP, are being utilized to protect patient safety, these events fall outside of the intent of the original protocol design, may have an impact on data interpretation, and thus will be characterized as protocol deviations for the purposes of data summary and analysis.

Any protocol deviations resulting from COVID-19 should be clearly identified as such within the protocol deviation description and summarised separately.

All deviations need to be documented in the participant's source records and placed in a dedicated COVID-19 folder. The site should continue to manage and submit protocol deviations per local requirements.

11.14.5.2. Capturing COVID-19 Specific AEs and SAEs

It is important for the study team to describe COVID-19 related adverse events/serious adverse and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.

2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.

3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events (related to COVID-19 infection), investigators should use the following Verbatim terms:
    a) Suspected COVID-19 infection; or
    b) Probable COVID-19 infection; or
    c) Confirmed COVID-19 infection

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.

5. A new COVID-19 infection Case Report Form will be added to the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important to collect the correct information from each participant reporting a COVID-19 AE or SAE. Therefore, please use the CRF templates to help you collect this information for all COVID-19 related AEs/SAEs, once available.

WHO Case Definition (March 20, 2020 Version) (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))**:**

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

11.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01, 26-MAR-2018

Overall Rationale for the Amendment: A global amendment applicable to all participating countries to clarify entry criteria, correct errors and improve consistency.

Section # and Name	Description of Change	Brief Rationale
Section 1.2: Schema Section 8.1.3: Exploratory Efficacy Endpoints Section 9.4.1: Efficacy Analyses	Changed DTG + 3TC to DTG/3TC FDC	To improve consistency
Section 1.3: Schedule of Activities (SoA)	X was removed at Week 4 and Week 52 for PK sampling	To correct an error in the original protocol
Section 2.3.1: Risk Assessment	Updated DTG: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations to add: 'A review of postmarketing data found that the number of cases reporting particularly severe liver dysfunction was found to be very low in the context of exposure to DTG and DTG/ABC/3TC. The reported cases of severe liver dysfunction (including acute hepatic failure) are complex with potential confounding factors but in a very small number of cases, drug-induced liver injury is likely and the role of DTG containing regimens cannot be ruled out particularly in those involving DTG with ABC/3TC or DTG/ABC/3TC.'	To provide updated language to further inform risk assessment
Section 4.1: Overall Design, Protocol Title, Short Title	Updated Phase IIIb to Phase III	To clarify study Phase
Section 5.1: Inclusion Criteria	Inclusion criterion 5 was updated to add 'or from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF)' to read 'A switch from a PI boosted with RTV to the same PI boosted with cobicistat is allowed (and vice versa). A switch from lamivudine (3TC) to emtricitabine (FTC) or from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) is also allowed (and vice versa).' Inclusion criterion 6 updated '30 days' to '28 days' to read 'A WOCBP who agrees to follow the	To clarify the study population intended to be enrolled; to align inclusion criterion 6 with the 28 day Screening period

Section # and Name	Description of Change	Brief Rationale
	contraceptive guidance in Section 11.3.2 during the treatment period from 28 days prior to the first dose of study medication and until the last dose of study medication and completion of the follow-up visit. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.'	
Section 5.2: Exclusion Criteria	Exclusion Criterion 5 was updated to add 'Participants with a documented history of chronic HBV and current undetectable HBV DNA while on a TAF/TDF regimen are excluded.' Exclusion Criterion 20 was updated to remove 'with the exception of Grade 4 lipid abnormalities' to read 'Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening period to verify a result.'	To clarify the study population intended to be enrolled

Amendment 02, 14-NOV-2018

Overall Rationale for the Amendment: A global amendment applicable to all participating countries to update the study design including length of study, updates to the eligibility criteria and removing the option to remain on the study if the participant becomes pregnant. Additional changes were made to manage and mitigate risks following identification of a potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir at the time of conception. A sub-study was added to collect data on participants who withdraw for meeting CVW or PVW criteria.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis Section 1.2, Schema Section 1.3, Schedule of Activities Section 2.1, Study Rationale Section 3, Objectives and Endpoints Section 4.1, Overall Design Section 4.2, Number of Participants Section 4.3, Participant and Study Completion Section 4.4, Scientific Rationale for Study Design Section 6.8, Treatment after the end of the study Section 7.2, Withdrawal from the Study Section 8.1.3, Exploratory Efficacy Endpoints	Study rationale updated based on shortened study design; minor updates to clarify several objectives and endpoints and removal of other objectives and endpoints to reflect updated study design; overall design section and Intervention groups and duration sections were updated to reflect a 52 week study. Participants on CAR will no longer switch at Week 52 as the study will end. Only participants in the D3 arm will have the opportunity to enter a continuation phase; number of participants section was updated to reflect current goal to include 20% women and include a goal of approximately 20% participants on efavirenz/emtricitabine/tenofovir disoproxil fumarate and approximately 20% aged ≥50 years; study schematic updated based on shortened study design; schedule of activities updated based on shortened study design; the SDM will now be collected every 24 weeks during the continuation phase to address shortened study design; updated SoA footnotes as required.	To reflect shortened study design from 104 weeks to 52 weeks
Section 1.3, Schedule of Activities Section 1.4, Pregnancy SoA Section 2.3, Risk/Benefit Assessment Section 4.1, Overall Design Section 4.3, Participant and Study Completion Section 4.4, Scientific Rationale for Study Design Section 6.8, Treatment after the end of the study Section 7.2, Withdrawal from the Study Section 8.2.6, Pregnancy Section 8.2.7, Infant Outcomes Section 8.2.8, Lactation Section 8.5, Pharmocokinetics Section 9, Statistical Considerations Section 11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Removed all text related to permitting participants to remain on study if they become pregnant; removed risk related to use in pregnancy as this is no longer permitted and added risk related to Neural Tube Defects; updated all sections to remove information related to PK sampling in pregnant participants; updated withdrawal criteria related to pregnancy; contraceptive guidance updated to remove double barrier method and collection of pregnancy information updated	To reflect updated study design to remove the option to remain on the study if the participant becomes pregnant; Updated to manage and mitigate risks following identification of a potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir at the time of conception.
Section 5, Study population	Inclusion criteria 5 and 6 and exclusion criterion 28 updated	To further clarify the study population
Section 1.1, Synopsis Section 4.1, Overall Design Section 7.1.1.2 Managing	Added reference to and details of new CVW or PVW sub-study	A CVW or PVW sub-study was added to collect

Section # and Name	Description of Change	Brief Rationale
Participants Meeting Precautionary Virologic Withdrawal (PVW) or Confirmed Virologic Withdrawal (CVW) Criteria Section 11.2, Appendix 2: A Sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or PVW Criteria		additional data on participants who withdraw from 208090 study for meeting CVW or PVW criteria
Section 8.8, Biomarkers Section 11.7, Appendix 7 Clinical Laboratory Tests	Updated to add Urine RBP/creatinine ratio and Urine B2M/creatinine ratio and clarify that RBP and B2M will be urine sample only and not blood	To further clarify what biomarkers will be collected during this study
Section 1.3, Schedule of Activities Section 8.10.1, HIV-1 Exploratory Analysis	Updated to add viral DNA quantitation and include language around collection of PBMCs/whole blood	To allow for additional Virology exploratory analysis
Section 11.9, Appendix 9: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart Guidelines	Liver safety requirements were updated	Updated to align with current ViiV Safety and Labelling Committee (VSLC) guidelines
Title Page, Authors Section 2, Introduction Section 2.2, Background Section 8.1, Efficacy Assessments Section 8.5, Pharmacokinetics Section 8.9 Health Economics and Outcomes Research Section 9, Statistical Considerations Section 10, References	Authors list updated to add PPD PPD and PPD and to remove PPD PPD and PPD ; Clarifying details regarding PK collection for overdose added; Section 8.9 Heading updated to include outcomes research; Table 2 updated to add recent studies and other minor changes; references updated	To reflect minor updates for clarity and additional recent data added for completeness

Amendment 03, 25-MAR-2019

Overall Rationale for the Amendment: A global amendment, for administrative purposes, applicable to all participating countries. Edits to increase clarity around collection of virology specimens for additional testing, the timing of the eCSSRS questionnaire in relation to medication administration, and follow-up for AEs were made. Additional changes were made to correct editing errors related to the tables for liver stopping criteria, which contained both GSK and ViiV-specific stopping criteria. This amendment removed the GSK information. No changes were made to the ViiV-specific criteria that was included in the previous version.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	Updated SoA footnote “d” for clarity	Add language for clarity
Section 7.1.2, Liver Chemistry Stopping Criteria	Removed algorithm and added verbiage to clarify when discontinuation of study intervention is required	Correction of editing errors inadvertently left in the previous protocol version Add language for clarity
Section 8.10.1, HIV-1 Exploratory Analysis	Clarified language around use of samples for additional testing	Add language for clarity
Section 11.9 Appendix 9: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart Guidelines	Clarified language for required actions and follow-up for liver events	Add language for clarity
Section 11.9.1, Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments	Removed duplicate criteria from table	Correction of editing errors inadvertently left in the previous protocol version
Section 11.9.2, Study Intervention Restart after Stopping for Liver Criteria	Updated Section title Clarified language for ViiV-specific criteria for restart after stopping for a liver event	Correction of editing errors Add language for clarity

Amendment 03/CHI-1, 31-MAY-2019

Overall Rationale for the Country-Specific Amendment: This is a country-specific amendment for administrative purposes applicable only to China. All edits removed those tests which are not able to be conducted in China due to laboratory limitations. These include collection of specific virology specimens for virological testing of linkage and minority species analyses, low level HIV-1 RNA quantitation, viral DNA quantitation, measurement of viral replicative capacity all biomarkers, and those of telomerase function and length. Additionally, in the event of any liver stopping events, the requirements for serum acetaminophen, and blood samples for pharmacokinetic (PK) analysis were deleted for the same reason.

Section # and Name	Description of Change	Brief Rationale
Section 8.8, Biomarkers	Removed all biomarkers	Will not be conducted in subjects at study sites in China. Remaining analytes/tests are medically necessary
Section 8.10, HIV-1 Polymerase Viral Genotyping and Phenotyping	Revised description of specific virology specimens and tests performed.	Will not be conducted in subjects at study sites in China. Those tests which remain are medically necessary and not for exploratory purposes.
Section 8.10.1, HIV-1 Exploratory Analysis	Section deleted.	Will not be conducted in subjects at study sites in China. Those tests which remain are medically

Section # and Name	Description of Change	Brief Rationale
		necessary and not for exploratory purposes.
Section 1.3, Schedule of Activities (SoA)	Deleted SoA list of tests and the accompanying footnotes bb,cc,dd,ee.and ff and updated order of footnotes accordingly	Revised to reflect only those tests to be conducted in subjects at study sites in China
Section 3. Objectives and Endpoints	Deleted phenotypic resistance; Exploratory section title revised to Tertiary. Revised row two objectives and endpoints and deleted row three information	Revised for clarity
Section 7.1.1.2., Managing Participants Meeting Precautionary Virologic Withdrawal (PVW) or Confirmed Virologic Withdrawal (CVW) Criteria	Deleted phenotype/phenotypic from section	Revised for clarity.
Section 8.1 Efficacy Assessments	Clarified HIV RNA quantification methods. Deleted text referring to exploratory analyses	Revised for clarity
Section 8.4, Treatment of Overdose	Removed text regarding plasma sample for PK analysis	Will not be conducted in subjects at study sites in China.
Section 8.5, Pharmacokinetics, subsections Liver Event and Overdose	Statements regarding plasma sample for PK analysis were deleted	Will not be conducted in subjects at study sites in China
Section 9.4.1. Efficacy Analyses and Section 9.4.2. Safety Analyses	Removed text referring to exploratory analyses	Revised for clarity
Section 11.2.2., Sub-study Objectives and Endpoints	Subtitle for Table revised to Tertiary, as this information from this substudy is of medical importance	Revised for clarity
Section 11.7 Appendix 7: Clinical Laboratory Tests, Table 5, Protocol Required Safety Laboratory Assessments	Revised table contents and footnotes	Revised to reflect only those tests to be conducted in subjects at study sites in China .
Section 11.9.1, Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments	Removed text and accompanying footnote regarding serum acetaminophen and blood sample for pharmacokinetic analysis	Will not be conducted in subjects at study sites in China .
Section 11.13, Country specific requirements	The rationale for making this amendment is provided.	All laboratory tests are required to be conducted within country.
Section 11.14, Protocol amendment history	All prior protocol amendments are listed.	Standard practice to list prior protocol amendments

Amendment 03/SWE-DEN-1, 29-JUL-2019

Overall Rationale for the Amendment: This is a country-specific amendment for administrative purposes applicable only to Sweden and Denmark. All edits were made to remove all reference to the Continuation Phase. Participants in both treatment arms will now finish the study at Week 52. This amendment was required for Sweden and Denmark to update the protocol with a clear time for the study´s conclusion based on scientific basis without any reference to market approval.

Section # and Name	Description of Change	Brief Rationale
Section 1: Protocol Summary, Section 1.2: Study Schematic, Section 1.3: Schedule of Activities and footnotes Section 2.3.1: Risk Assessment, Section 3: Objectives and Endpoints Section 4.1: Overall Design Section 4.3: Participant and Study Completion Section 6.7: Concomitant Therapy Section 6.8: Treatment after the end of the study Section 7.1: Discontinuation of study intervention Section 11.13: Appendix 13, Country Specific Requirements	The continuation phase was removed from all applicable sections of the protocol.	This amendment was required for Sweden and Denmark to update the protocol with a clear time for the study´s conclusion based on scientific basis without any reference to market approval.