Protocol Amendment 04

Study ID: 208379

Official Title of Study: A Phase IIb, randomized, partially blind, active controlled, dose-range finding study of GSK3640254 compared to a reference arm of dolutegravir, each in combination with nucleoside reverse transcriptase inhibitors, in HIV-1 infected antiretroviral treatment-naive adults

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TITLE PAGE

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Protocol Number: 208379/ Amendment 04

Compound Number:	GSK3640254

Study Phase: Phase 2b

Short Title: A Phase 2b Dose-Range Finding Clinical Trial in HIV-1 Infected Treatment-Naive Adults

Acronym: DOMINO

Sponsor Name and Legal Registered Address (excluding US):

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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 is supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information

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PPD
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Regulatory Agency Identifying Number(s):

IND #: 139,838

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Approval Date: 01-OCT-2021

SPONSOR SIGNATORY

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Max Lataillade, DO, MPH Vice President, Head of Global Research Strategy ViiV Healthcare	**Date**

The signed page is a separate document.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Global Amendment 04	*01-OCT-2021*	TMF-13994091
Global Amendment 03	*10-MAY-2021*	TMF-12472318
Global Amendment 02	*09-APR-2021*	TMF-11948442
Site Specific Protocol SS 1-244689	*11-DEC-2020*	2019N399207_04
Global Amendment 01	*25-SEP-2020*	2019N399207_03
Country Specific Protocol POR-1	*18-SEP-2020*	2019N399207_02
Country Specific Protocol CAN-1	*18-SEP-2020*	2019N399207_01
Original Protocol	*29-MAY-2020*	2019N399207_00

Amendment 04: 01-OCT-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Study 208379 is undergoing this non-substantial amendment primarily to modify further the minimum number of CD4+ T-cells needed for study inclusion. Sponsor continues to try to find ways to improve the pace of recruitment without compromising safety of the participants nor the basics tenets of the research.

The trial began screening in November in 2020, and Sponsor intially anticipated screening 210 participants would complete by 18 May 2021. However, at the time of this substantial amendment approximately 275 participants have been screened and approximately 85 have been randomized, in the study now looking to recruit only 150 total. The reasons for the slow pace of recruitment are based upon the multi-factorial impact of the global Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) pandemic. Qualitative feedback from Investigators shows the incidence of known, newly diagnosed Human immunodeficiency virus-1 (HIV-1) infection has decreased. Moreover, physicians and newly infected patients have a strong desire to immediately start antiretroviral therapy so they are less likely to participate in this Phase 2b study that has a screening period of approximately 42 days.

Additional modifcations are included for accuracy, consistency and transparency.

Section # and Name	Description of Change	Brief Rationale
Cover page	Inserted contact information for the additional Medical Monitor	To meet the needs of an expanding GSK3640254 program.
1.1, Synopsis, Overall Design 5.1, Inclusion Criteria, #4	Modified the CD4+ T-cell count needed to meet eligibility, lowered from 300 to 250	To improve eligibility and recruitment without compromising safety.
1.1, Synopsis, Intervention Groups and Duration	Modified the randomization ratio from 2:2:2:1 to "approximately 1:1:1:1" to align with the changes in the number of participants in the GSK3640254 treatment arms made by Protocol Amendment 03.	For accuracy. This was erroneously omitted from Protocol Amendment 03.
4.1.5, Optional Stomach Substudy (Esophagogastroduodenoscopy [EGD] with Biopsy and Serum Biomarkers)	Inserted the word "approximately" in reference to the number of substudy participants expected from each treatment arm (7) as well as the total number of participants (28). Because the GSK3640254 treatment arms are blinded, it will be unknown to the blinded team at the time of recruitment end if the arms filled evenly. Additionally, the total number of participants in this substudy may fall short of the desired total of 28, even if recruitment stays open (as described in Section 4.1.5.1).	For transparency. Given the challenges to date of trying to recruit this study during the global pandemic, protocol language is needed to address a possible substudy recruitment shortfall.
4.1.5.1 Stomach Substudy Enrollment Considerations	Inserted a statement to indicate the substudy may be allowed to overenroll if needed to account for any prior substudy discontinuations.	For transparency.
5.2, Exclusion Criteria #35	Removed Grade 4 ALT from the list of parameters that could be considered for inclusion. This was in direct conflict with the FDA-required ALT exclusion set forth in Exclusion Criterion #26: ALT ≥3 x ULN, which is the equivalent of Grade 2 or higher. If a Screening ALT test result ≥ Grade 2, it can be repeated within a Screening period.	For accuracy.

Section # and Name	Description of Change	Brief Rationale
5.3.3, Activity	Removed unnecessary text regarding the limited description of any allowed light activity. The first sentence in this section, indicating that strenuous activity is prohibited within 24 hours of a study clinic visit, is sufficient.	For accuracy.
6.3, Measures to Minimize Bias: Randomization and Unblinding	Inserted details regarding controlled access to PK and PKPD data during the blinded phase of the study.	For transparency.
8.2.3, Cardiac Monitoring with Electrocardiograms	Removed the statement that indicated sites could request an overread by an ERT cardiologist at any time. This cannot be accommodated due to the manner in which the study is set up with ERT.	For accuracy.
8.2.6, Suicidal Ideation and Behaviour Risk Monitoring	Corrected the description of the visit at which the Lifetime assessment of the eCSSRS is performed.	For accuracy.
9.3.3, Pharmacokinetic Population	Inserted a statement that makes reference to new details added in Section 6.3.	For consistency among the 2 related sections of the protocol..
9.3.4, Safety Population	Removed the table that provided definitions for the Enrolled and Randomized populations. This table had been misplaced; these 2 populations are not part of the Safety population.	For accuracy. While some systems use the word “enrolled” to mean those who have Screened, an “enrolled” population may have a different definition in guidance for statistical analyses.
9.3.5, Screened Population	Moved the definition of the Enrolled population from Section 9.3.4 to this new section, and renamed it to be the Screened population.	For accuracy.
9.3.6, Randomized Population	Moved the definition of the Randomized population from Section 9.3.4 to this new section.	For accuracy.
9.5, Interim analyses	Inserted a statement to indicate when and how additional data cuts and analyses may occur.	For transparency, as the need for an interim analysis can arise at any time.

Section # and Name	Description of Change	Brief Rationale
10.3.5, Reporting SAE to Sponsor	Removed the requirement for Investigators to enter SAE Causality within 72 hours. New instruction was inserted.	To align with GSK/ViiV's removal of this requirement.
10.11.4, COVID-19 Therapeutic Agents	Replaced the word "experimental" with the word "therapeutic" to describe the agents now available to treat COVID-19.	To align with research and development of treatments for COVID-19.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase IIb, randomized, partially-blind, active-controlled, dose-range finding study of GSK3640254 compared to a reference arm of dolutegravir, each in combination with nucleoside reverse transcriptase inhibitors, in HIV-1 infected, antiretroviral treatment-naive adults

Brief Title:

A Phase 2b Dose-Range Finding Clinical Trial in HIV-1 Infected Treatment-Naive Adults

Rationale:

Infection with HIV-1 continues to be a serious health threat throughout the world, with more than 40 million individuals infected worldwide. The current standard of care treatment for HIV-1 is combination anti-retroviral therapy (cART) with recommendations to start regardless of CD4 T-cell count, committing people living with HIV to lifelong, life-saving therapy. However, the chronic exposure to cART has identified anti-retroviral (ARV)-associated long-term toxicities (e.g. central nervous system (CNS) or cardiovascular (CV)/metabolic effects, renal disease, etc.), creating a need to address and prevent these co-morbidities. Also, treatment failure remains a continuing concern in clinical care due to the presence and emergence of resistant strains and tolerability issues. The aging HIV-1-infected population drives a need for drugs with fewer drug-drug interactions. In this environment, medicines with novel mechanisms of action (MoA) that can be used as part of a preferred cART regimen have an important role to play. However, to be successful, a new ARV agent must be safe and effective, provide a relatively high barrier to resistance, have low toxicity, have minimal drug-drug interactions, and preferably be a relatively low-dose, once-a-day drug that can be combined with other agents as part of a fixed-dose regimen. GSK3640254, a next generation HIV-1 maturation inhibitor (MI), has the potential to meet such valued features for a new ARV medicine.

GSK3640254 is a next-generation HIV-1 MI that binds near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton (kDa) HIV capsid (CA) protein p24 (CA [p24]) and spacer peptide 1 (SP1). Blockage at this step results in the release of immature non-infectious virus particles. Other small molecules within this class have demonstrated a Pharmacokinetic (PK)/Pharmacodynamic (PD) relationship and longer-term efficacy through Phase 2a-2b trials.

At the time of this protocol submission, GSK3640254 has completed a short-term, monotherapy, proof of concept (POC) Phase 2a study. Additionally, the safety, tolerability, and PK have been evaluated in eight other completed Phase 1 studies in

healthy volunteers. The totality of the clinical data shows: 1) GSK3640254 is generally well-tolerated in short-term studies and 2) GSK3640254 has a short-term PK/PD (decline in HIV-1 RNA) relationship.

The Sponsor proposes conducting this Phase 2b dose-range finding study, the primary objective of which is to evaluate the efficacy in a Randomized Phase of GSK3640254 relative to dolutegravir (DTG), each given in combination with abacavir/lamivudine (ABC/3TC) or emtricitabine/tenofovir alafenamide (FTC/TAF) for the selection of an optimal dose, by analysing the proportion of Virologic Responders (HIV-1 RNA <50 copies/mL at Week 24). Secondary objectives are to evaluate: 1) longer term efficacy, 2) key safety/tolerability, 3) cumulative PK, and 4) cumulative resistance. These secondary objectives will also be evaluated in a Non-Randomized Phase when the NRTI backbone is switched to DTG (in the experimental arms only) after the last subject completes their Week 48 visit. The totality of this data would inform the basis of subsequent clinical trials in HIV-1 infected patients.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate antiviral efficacy of GSK3640254 relative to DTG, each given in combination with 2 NRTIs, enabling the selection of an optimal dose for GSK3640254	• Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24 using the FDA snapshot algorithm
Secondary Efficacy, Safety and PK	
• To evaluate antiviral efficacy in the Randomised Phase of GSK3640254 relative to DTG, each given in combination with 2 NRTIs at Week 48 • To evaluate antiviral efficacy in the Non-Randomised Phase of GSK3640254 optimal dose given in combination with DTG relative to the reference arm (DTG given in combination with 2 NRTIs) at Week 96	• Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Weeks 48 and 96 using the FDA snapshot algorithm • Absolute values and changes from baseline in HIV-1 RNA through Weeks 24, 48, and 96 • Absolute values and changes from baseline in CD4+ cell counts through Weeks 24, 48, and 96
• To evaluate safety and tolerability in the Randomised Phase of GSK3640254 relative to DTG, each given in combination with 2 NRTIs at Weeks 24 and 48 • To evaluate safety and tolerability in the Non-Randomised Phase of GSK3640254 optimal dose given in combination with DTG relative to the reference arm (DTG	• Frequency of SAEs, Deaths and AEs leading to Discontinuation through Weeks 24, 48, and 96 • Incidence and severity of AEs through Weeks 24, 48 and 96 • AEs in GI, Psych/CNS through Weeks 24, 48, and 96

Objective	Endpoint
given in combination with 2 NRTIs) at Week 96	
• To assess the development of viral resistance in the Randomised Phase to GSK3640254 and 2 NRTI backbone in participants experiencing virologic failure at Weeks 24 and 48. • To assess the development of viral resistance in the Non-Randomised Phase to GSK3640254 and DTG in participants experiencing virologic failure at Week 96.	• Changes in genotypic and/or phenotypic profiles of virus compared to baseline through Weeks 24, 48, and 96
• To characterize the pharmacokinetics of GSK3640254 when given in combination with ABC/3TC or FTC/TAF	• The steady-state plasma PK parameters of GSK3640254 will be assessed based on Intensive and/or Sparse PK sampling through Weeks 24 and 48.

Overall Design:

Study 208379 is a Phase 2b, randomized, partially blind (to GSK3640254 dose), active controlled clinical trial to investigate the safety, efficacy and dose-response of GSK3640254 compared to DTG, each given in combination with 2 NRTIs, in approximately 150 treatment-naïve HIV-1 infected adults.

The Sponsor will be blind to the dose of GSK3640254 treatment (being evaluated for the treatment of HIV-1) allocation until the database lock for the Week 24 analysis. The primary analysis will evaluate all available data as outlined in the endpoints for primary and secondary objectives. The primary analysis will result in the selection of an optimal dose of GSK3640254. After an optimal dose is selected by the Sponsor, a communication will be sent to Health Authorities/Ethics Committees, where required or requested, for their information. Investigators and participants will be unblinded to participant's initial dose as well as to the optimal dose of GSK3640254 after the last participant completes their Week 48 visit. The Randomised Phase will be complete after the last participant completes their Week 48 visit. In the Non-Randomised Phase, participants in the GSK3640254 Arms with their most recent HIV-1 RNA <50 c/mL will change from their blinded GSK3640254 dose to the open label, optimal dose of GSK3640254 and, at the same time, they will switch from their open label, dual NRTI backbone to open label DTG. Participants in the GSK3640254 Arms with their most recent HIV-1 RNA = 50-199 c/mL may be able to make this change as well, but only after site's consultation with the ViiV medical monitor, else they will be discontinued from the study. This change from dual NRTI to DTG will provide additional clinical and scientific data on the maintenance of virologic suppression, safety/tolerability, and treatment emergent resistance if, in subsequent clinical trials, GSK3640254 is only administered with DTG.

All medications in the reference arm will be open label throughout both phases. Participants in the reference arm will end their participation in the treatment phase as each individual participant reaches their Week 144 visit.

The most clinically relevant inclusion/exclusion criteria are as follows: Participants must have an HIV-1 RNA ≥1000 c/mL and a CD4 T-cell count ≥250 cells/mm^3. Participants must not have received any ARVs, in combination or monotherapy, after the diagnosis of HIV-1. Participants will be excluded if they are co-infected with Hepatitis B or C, have significant psychiatric condition, have a significant gastrointestinal (GI) condition (including inability to eradicate *Helicobacter pylori*) or have a cardiac condition which places them at greater risk for QT prolongation.

Brief Summary:

Approximately 150 treatment-naïve, HIV-1 infected adult will be randomized into this Phase 2b dose-range finding study, the primary objective of which is to evaluate the efficacy of GSK3640254 relative to DTG, each given in combination with 2 NRTIs, by analysing the proportion of virologic responders: participants with HIV-1 RNA <50 c/mL at Week 24. Participation will be for at least 24 weeks, then up to 96 weeks or more. Participants will be followed at visits every 4 weeks during the first year, then at increasing intervals in the years following. Access to the study treatments will be maintained in this study, or in a rollover study, until GSK3640254 is locally approved and commercially available; participants in the reference arm, however, will end their participation in the treatment phase as each individual participant reaches their Week 144 visit.

Number of Participants:

Approximately 300 participants will be screened to achieve approximately 150 randomly assigned to one of 4 arms of the study interventions, approximately 40 per GSK3640254 arm, and approximately 30 in the DTG Reference Arm.

The enrollment period may be extended if the additional effort is needed to help ensure a sufficient number participate in the optional Stomach Substudy.

Intervention Groups and Duration:

Participants will enter the Screening period for a maximum of 42 days, and if they qualify, will be randomly assigned to receive either GSK3640254 or DTG, plus an investigator-selected choice among 2 dual-NRTI background therapies (ratio of approximately 1:1:1:1) for a period of at least 48 weeks in the Randomised Phase:

- Arm 1: Blinded GSK3640254 100 mg + Open Label ABC/3TC or FTC/TAF
- Arm 2: Blinded GSK3640254 150 mg + Open Label ABC/3TC or FTC/TAF
- Arm 3: Blinded GSK3640254 200 mg + Open Label ABC/3TC or FTC/TAF
- Arm 4: Open Label DTG + Open Label ABC/3TC or FTC/TAF

Participants will be stratified by Screening plasma HIV-1 RNA, by <100,000 c/mL or ≥100,000 c/mL, and the investigator's choice of dual NRTI background therapy (either ABC/3TC or FTC/TAF).

Participants in any arm who are Virologic Responders may continue in the study beyond Week 24.

In the experimental arms, GSK3640254 will be administered in 3 blinded doses until the last participant completes their Week 48 study visit (Week 48 Secondary Endpoint study milestone). Thereafter, participants whose most recent HIV-1 RNA <50 c/mL in the GSK3640254 arms will move into the Non-Randomised Phase and will be switched from their blinded dose to the open label optimal dose. Simultaneously, these participants will also be switched from their dual NRTI therapy to DTG. Participants in the GSK3640254 Arms with their most recent HIV-1 RNA = 50-199 c/mL may be able to make this change as well, but only after site's consultation with the ViiV medical monitor, else they will be discontinued from the study.

Thereafter, the trial will be fully open label with just 2 arms:

- Arms 1, 2 & 3 will switch to the Open Label GSK3640254 Optimal Dose + Open Label DTG
- Participants on the Open Label DTG + ABC/3TC or FTC/TAF arm will continue unchanged into the Non-Randomised Phase

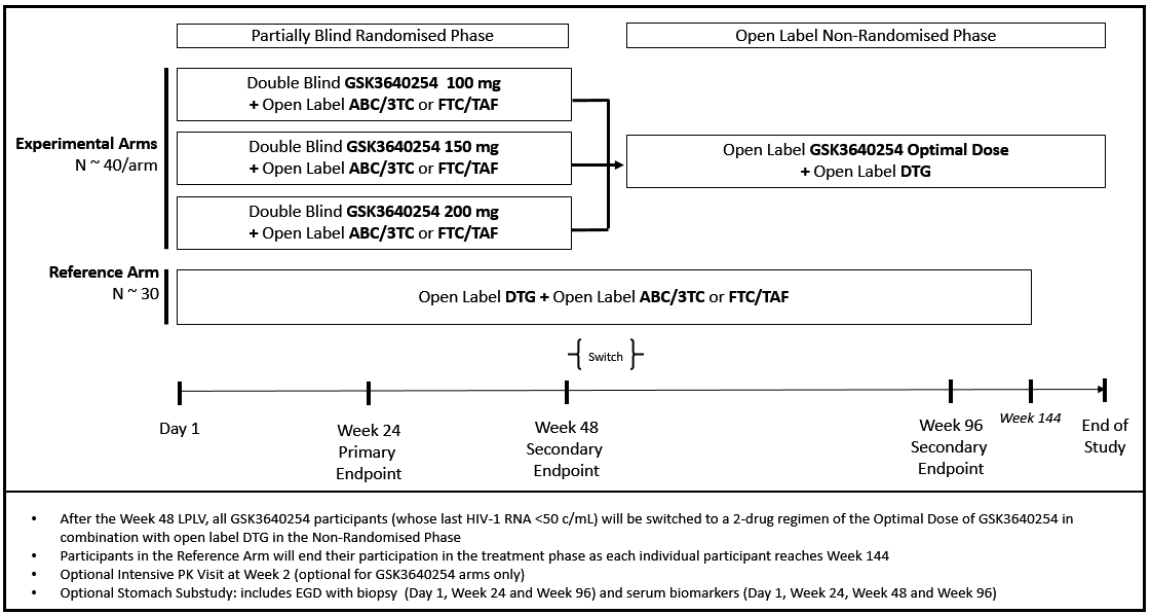
Participants who continue to derive benefit from the treatments will remain on study beyond Week 96, in this study or in a rollover study, until GSK3640254 is commercially available (projected to be in the year 2027) or they are transitioned onto a local access program; participants in the reference arm, however, will end their participation in the treatment phase as each individual participant reaches their Week 144 visit.

Independent Data Monitoring Committee:

The study will include an Independent Data Monitoring Committee.

The IDMC will review the totality of clinical data (exclusive of the Stomach Substudy) with at least one analysis before the Week 24 Primary Analysis and will be responsible for recommending to the Chief Medical Officer (CMO) and the ViiV Safety and Labelling Committee (VSLC): 1) discontinuation of any treatment arm, 2) discontinuation of the study, or 3) continuation of the study as planned. Moreover, a separate IDMC recommendation from a parallel Phase 2b Study 212483 (same doses of GSK3640254 + DTG in HIV-1 infected treatment naïve adults) may impact the CMO and VH Governance decision-making on any arm(s) within this trial.

1.2. Schema



- After the Week 48 LPLV, all GSK3640254 participants (whose last HIV-1 RNA <50 c/mL) will be switched to a 2-drug regimen of the Optimal Dose of GSK3640254 in combination with open label DTG in the Non-Randomised Phase
- Participants in the Reference Arm will end their participation in the treatment phase as each individual participant reaches Week 144
- Optional Intensive PK Visit at Week 2 (optional for GSK3640254 arms only)
- Optional Stomach Substudy: includes EGD with biopsy (Day 1, Week 24 and Week 96) and serum biomarkers (Day 1, Week 24, Week 48 and Week 96)

1.3. Schedule of Activities (SoA)

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
Clinical Assessments														
Informed Consent	X	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV		NV	NV = if a New Version is available
Inclusion/Exclusion criteria	X	X												Review during Screening; Confirm prior to Day 1 dose.
Demography	X													
Height, Weight, and BMI	X	W	W	W	W	W	W	W	W	W	W		W	W = weight only
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X	Section 8.2.2

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
Physical Exam		F				T			T	T at Week 48, 96	T at Week 120 then every 6 months		T	F = Full Physical T = Targeted Physical See Section 8.2.1
Medical History[3]	X													
Current Medical Conditions	X													
Prior ARV Check	X													Ensure naïve status
CDC HIV-1 Classification	X	X												Section 10.10
HIV-associated conditions	X	X	X	X	X	X	X	X	X	X	X	X		

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
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Adverse event (AE)/SAE assessments	SAE Only	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Concomitant medications review[4]	X	X	X	X	X	X	X	X	X	X	X	X		Section 6.8
Adherence Review[5]			X	X	X	X	X	X	X	X	X	X		
C-SSRS – *Baseline/Lifetime*	X													See Section 8.2.6
C-SSRS – *Since Last Visit*		X	X	X	X	X	X	X	X	X	X	X[6]		See Section 8.2.6
Clinical Procedures														
ECG: single reading	X										at EW only			

Activities[1]	**Screening**	**IN-CLINIC VISITS[2]**										**VIRTUAL VISIT[2]**	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
ECG: single reading PRE-dose			X											See Section 8.2.3 Post-dose ECGs are to be done ±15 minutes of the time point
ECG: **triplicate** readings PRE-dose		X												
ECG: single readings POST-dose at 2, 4 and 6 hours		X	X											
ECG: single reading POST-dose any time between 2-6 hrs						X			X	Weeks 36 and 48, 72, 96	X (not at EW)			

Optional Stomach Substudy[7] Esophagogastroduodenoscopy (EGD) with biopsy		X[7]							X	Week 96[8]				See Section 4.1.5 and Section 8.6.1; Separate Stomach Substudy ICF The "Day 1" EGD with biopsy procedure, in most cases, needs to be done *prior to* Day 1 within the Screening period. The Day 1 Substudy biomarkers are to be drawn at the Day 1 visit.
Clinical Assessments														
Urine Drugs of Abuse panel	X													Also, for any Grade 3-4 Psychiatric AE. See Section 8.2.6
*HLA-B*5701* allele	X													

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
PT/INR	X													For Child-Pugh per Section 10.7
Rapid Plasma Reagin (RPR)	X													
Local lab breath or stool test for *Helicobacter pylori*[4]	X										EW or Final visit only			See Section 4.1.1 To be done at the site's local lab
Pregnancy test[9]	S	U, S		S	S	S	S	S	S	S	S	U done at home	X	POCBP Only S = Serum U = Urine
Hematology/Chemistry	X	X		X	X	X	X	X	X	X	X		X	

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
Fasting Lipids[10]	X	X				X			X	Week 48, 72, and 96	Week 120, then every 6 months + Final/EW			6hr minimum fast.
Urinalysis	X	X		X	X	X	X	X	X	X	X		X	
Hepatitis B and C serology	X									Week 48 and 96	Week 144, 192, etc.			
HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X			
Lymphocyte T-cell subsets	X	X		X	X	X	X	X	X	X	X			CD4 and CD8
Plasma for Storage	X	X	X	X	X	X	X	X	X	X	X			

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
Plasma for Geno/Phenotypic Resistance Assays[11]	X	X		X	X	X	X	X	X	X	X			
PK – Sparse; GSK arms only				X	X	X			X	Week 36 and 48				See Section 8.4 Separate lab kit for Sparse PK contains a PRE-DOSE tube.
PK – Intensive; subset of participants in the GSK arms only Optional[12]			X											See Section 4.1.2.1.1 See Section 8.4 Separate lab kit for Intensive PK contains a PRE-DOSE tube.

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
Optional PGX sample[13]					X									Separate PGX ICF
Renal, Bone and Inflammatory biomarker analytes (blood/urine) and HbA1c, insulin and glucose[14]		X							X	Week 48 and 96	Week 144			
Optional Stomach Substudy[7,10] Fasting Serum Biomarkers		X							X	Week 48 and 96[8]				See Section 8.6.1; 12hr minimum fast Separate Stomach Substudy ICF; Separate lab kit

Activities[1]	**Screening**	**IN-CLINIC VISITS**[2]										**VIRTUAL VISIT**[2]	**IN-CLINIC Follow-up Visit**	**Notes**
	42 days *(or up to 63 days in certain situations)*	**Day 1**	**Wk 2** **Day 11-14**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Weeks 28, 32, 36, 40, 44, 48, 52, 56, 64, 72, 80, 88, and 96**	**Week 108 then every 12 weeks and Final Visit / Early Withdrawal (EW)**	**Week 60, 68, 76, 84, 92, 100 then every 4 weeks between in-clinic visits (Wk 104, 112, 116, etc.)**	*2-4 weeks after the last dose*	
Study Treatment														
RAMOS Enrol	X													
RAMOS Randomization/Study Treatment Assignment and Dispensation		X												
RAMOS Study Treatment Dispensation				X	X	X	X	X	X	X[15]	X (not at EW)			
RAMOS Final Disposition	SF										W at EW		C	S: Screen Fail W: Withdrawn C: Complete
Study Treatment Accountability (pill counts)			X	X	X	X	X	X	X	X	X			

1. Order of Assessments (pre-dose): CSSRS – ECG – Vital Signs – Blood Draws (see notes in Section 8.4 regarding order for blood draw and ECG during the Week 2 visit)

2. The acceptable window around any visit, Week 4 and beyond (including the Virtual Visits), is ± 2 days. Participant must come in no later than +2 days of the visit windows or participant will run out of drug supply.
3. Medical History includes substance usage and the Medical Conditions listed in Exclusion Criteria in Section 5.2 , as well as assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), and, in particular, but not limited to, cardiac, psychiatric, renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
4. The Concomitant Medication review at Screening includes not only those listed in Section 6.8 to be considered relative to dosing requirements, but also a check for prohibited medications (See Section 6.8.1) that may need to be stopped in order to meet the requirements of the local test for *H. pylori*.
5. Adherence review includes pill count, review of any recorded missed doses, and a conversation about other possible missed doses if the pill count does not match those recorded and/or verbally reported.
6. On Day 1, participants will provide response to the CSSRS Baseline form ***prior to*** the RAMOS task of Randomization. The CSSRS will be in electronic format, responses provided by participants either by phone or computer, whether they are in clinic or if they are remote (virtual visits).
7. Likely to be done at select countries/select sites. Participation in the Optional Stomach substudy includes both the EGD procedure with biopsy and the Serum Biomarker blood draws. For EGD procedure scheduling issues, the Screening period can be extended (See Section 5.5). Potential participants must undergo pre-procedural evaluation and consent with the GI facility at each time point. The Day 1 EGD procedure cannot be done on the same day as the Day 1 clinic visit, so it should be done during the Screening phase only when all lab assessments and procedures indicate that the participants qualifies for the study. See more details in Section 4.1.5. It is reasonably expected that the procedure should be performed ± 2 weeks around the Week 24 and Week 96 visit milestones. The frequency of additional Serum and EGD monitoring (e.g. Week 48, Week 144, etc.) will be based upon emerging clinical and scientific data solely from this trial.
8. Evaluations beyond Week 96 may be performed based upon emerging clinical / scientific data
9. At Screening, and for POCBP only, sites will submit serum for FSH and Estradiol, and for Pregnancy testing. (FOR CANADA ONLY: If the Day 1 visit does not occur within 30 days of the Screening Visit, a second serum pregnancy test [done approximately Day -7 to Day -5] should be performed so that results are known prior to the planned Day 1.) On Day 1, in addition to the serum sample sent to the central lab, a urine pregnancy test will be done in the clinic to confirm negative status prior to IP administration. If the urine test result is ambiguous, the site should await the results of the Day 1 serum test before study treatment can be initiated. On Treatment, a blood sample will be collected at each visit for serum pregnancy testing. Urine pregnancy tests will be done at every 4 weeks at home for the virtual visits (results need to be reported to the site). Any ambiguous urine result will need to be retested in serum. Site will provide tests kits to POCBP to be used in the interval (e.g., at Week 56, provide 1 test kit to be done at home at Week 60 Virtual Visit; at Week 108, provide 2 test kits to be done at home at Week 112 and Week 116 Virtual Visits).
10. An overnight fast is preferred prior to visits that include lipid and renal/bone/inflammation biomarker assessments, but a minimum of 6 hours is acceptable. Regardless of lipid collection, participants taking part in the Stomach Substudy should fast for a minimum of 12 hours prior to the collections at Day 1, Week 24, Week 48 and Week 96.
11. Unused plasma samples collected for the potential need of resistance testing will enter long-term storage and are then included in the pool of samples that can be used for further research, if participant has consented.
12. If there are COVID-19 impacts that restrict the ability for a participant to come to the clinic for the day-long visit at Week 2, then, at the least, all subjects should attend the clinic visit for the collection of HIV-1 RNA and as many of the ECGs as possible, and the Intensive PK portion of the visit for those in the GSK3640254 arms who opted to take part can be done at Week 16.
13. The earliest visit at which the PGX sample should be collected is at Week 8, or, if missed at Week 8, at a visit thereafter.
14. 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 and 25 Hydroxy-Vitamin D; **Inflammation:** Interleukin-6 (IL-6), High-sensitivity C reactive protein (hs-CRP), D-dimer, Soluble CD14 (sCD14), Soluble CD163 (sCD163); insulin and glucose for [redacted] calculation.

15. During the Randomized (blinded) Phase, the RAMOS NG system is programmed to dispense only a one-month supply of blinded GSK3640254 (set of 3 bottles). Therefore, starting at Week 56 (when the 8-week visit intervals begin), participants will need to come to the clinic monthly between clinic visits purely for a dispensation of blinded GSK3640254. For example, at Week 56, participant will receive a one-month supply, then they will need to come to the clinic near the Week 60 time point for dispensation; they will receive another one-month supply at their Week 64 clinic visit, then they will need to come to the clinic near the Week 68 time point for a dispensation, etc.

2. INTRODUCTION

Infection with HIV-1 continues to be a serious health threat throughout the world, with more than 40 million individuals infected worldwide. The current standard of care (SOC) treatment for HIV-1 is combination anti-retroviral therapy (cART) with recommendations to start regardless of CD4 cell count, committing people living with HIV to lifelong, life-saving therapy [European AIDS Clinical Society Guidelines, October 2020]. However, the chronic exposure to cART has identified anti-retroviral (ARV)-associated long-term toxicities (e.g. central nervous system (CNS) or cardiovascular (CV)/metabolic effects, renal disease, etc.), creating a need to address and prevent these co-morbidities. Also, treatment failure remains a continuing concern in clinical care due to the presence and emergence of resistant strains and tolerability issues. The aging HIV-1-infected population drives a need for drugs with fewer drug-drug interactions. In this environment, medicines with novel mechanisms of action (MoA) that can be used as part of a preferred cART regimen have an important role to play. However, to be successful, a new ARV agent must be safe and effective, provide a relatively high barrier to resistance, have low toxicity, have minimal drug-drug interactions, and preferably be a relatively low-dose once-a-day drug that can be combined with other agents as part of a fixed-dose regimen. GSK3640254, a next generation HIV-1 maturation inhibitor (MI), has the potential to meet such valued features for a new ARV medicine.

GSK3640254 is a next-generation HIV-1 MI which binds near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton (kDa) HIV capsid (CA) protein p24 (CA [p24]) and spacer peptide 1 (SP1). Blockage at this step results in the release of immature non-infectious virus particles. Other small molecules within this class have demonstrated a Pharmacokinetic (PK)/Pharmacodynamic (PD) relationship and longer-term efficacy through Phase 2a-2b trials.

As of February 2021, GSK3640254 has completed a Phase 2a study (short-term, monotherapy, proof of concept [POC]). Additionally, the safety, tolerability, and PK have been evaluated in eight other completed Phase 1 studies in healthy volunteers. The totality of the clinical data shows: 1) GSK3640254 is generally well-tolerated in short-term studies, and 2) GSK3640254 has a short-term PK/PD (decline in HIV-1 RNA) relationship. Summaries of the pre-clinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number 2018N379610_02].

2.1. Study Rationale

The Sponsor proposes conducting the Phase 2b dose-range finding study, the primary objective of which is to evaluate the efficacy of GSK3640254 relative to dolutegravir (DTG), each given in combination with either abacavir/lamivudine (ABC/3TC) or emtricitabine/tenofovir alafenamide (FTC/TAF), by analysing the proportion of Virologic Responders: participants with HIV-1 RNA <50 c/mL at Week 24. Secondary objectives are to evaluate: 1) longer-term efficacy, 2) key safety/tolerability, 3) cumulative PK, and

4) cumulative drug resistance. These secondary objectives would also be evaluated when the NRTI backbone is switched to DTG (in the experimental arms only) after the last subject completes their Week 48 visit. The totality of this data would inform the basis of subsequent clinical trials in HIV-1 infected patients.

2.2. Background

2.2.1. Key Safety Data with a Prior Maturation Inhibitor (GSK3532795)

Previously, ViiV Healthcare (VH) studied a structurally similar MI, GSK3532795, in the Phase 2b study 205891. The Week 24 primary endpoint analysis showed GSK3532795 was not optimal for Phase 3 development due to gastrointestinal (GI) intolerability and treatment-emergent resistance. Specifically, a relatively higher rate of GI intolerability (predominately Grade 1-2 diarrhea in 38-61% of participants and abdominal pain in 8-22% of participants) and higher rate of nucleoside reverse transcriptase inhibitor (NRTI) resistance (6.5%) with clinically significant changes in GSK3532795 susceptibility was observed across all three GSK3532795 treatment arms [Morales-Ramirez, 2018]. Given these clinical and tolerability issues, the Sponsor terminated study 205891 and did not advance GSK3532795 into Phase 3 studies.

Aside from mild to moderate GI intolerability, 2 serious adverse events (SAEs) occurred in the Phase I Thorough QT study AI468044/206220 [BMS Document Control Number 930109388] at supra-therapeutic doses: 1 healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The 2 participants received GSK3532795 240 mg twice daily and 240 mg once daily (QD) with food, respectively. These events were assessed as related to study drug but were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric adverse events (AEs) in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia, abnormal dreams).

Importantly, neither of these GI or psychiatric safety findings have been reproduced in the completed or ongoing clinical trials of GSK3640254 in healthy volunteers or HIV-1 infected treatment-naïve participants.

2.2.2. Preclinical Summary with GSK3640254

Nonclinical pharmacology and virology

Activity toward a panel of clinical isolates was similar among subtypes, with median 50% inhibitory effect (EC_{50}) values of 2.0 and 3.0 nM, for subtypes B and C, respectively, and 3 nM for subtypes A and CRF01_AE. GSK3640254 was active against 1 of 3 human immunodeficiency virus type-2 (HIV-2) isolates (EC_{50} = 2.5 nM). Based upon in vitro potency, GSK3640254 is projected to demonstrate efficacy toward the majority of subtype B, C and CRF01_AE isolates at a trough concentration (C_{trough}) value of 150 nM. Data suggest that GSK3640254 may be used in combination therapies with agents from any of the nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase strand transfer inhibitor (INSTI) and protease inhibitor (PI) antiretroviral (ARV) classes.

Mechanism studies indicate that GSK3640254 blocks production of infectious virus by specifically inhibiting HIV-1 protease-mediated cleavage at the CA (p24)/SP1 junction. GSK3640254 specifically binds to purified HIV-1 VLPs (Ki 0.7 nM) and dissociates slowly, with a half-life of 6 h. These mechanistic studies confirm that GSK3640254 inhibits via a novel mechanism of action (MoA) that is distinct from current ARVs. The A364V amino acid substitution was the most common change selected by GSK3640254 in cell culture resistance selection experiments, appearing in several different group-specific antigen (Gag) polymorphic backgrounds.

Pharmacokinetics and product metabolism in animals

Following intravenous (IV) administration, GSK3640254 exhibited low systemic clearance, high volume distribution, and elimination half-lives of 5.06, 4.0, 18.7 and 5.3 h in mouse, rats, dogs and monkeys, respectively. GSK3640254 was eliminated mainly by direct glucuronidation followed by biliary excretion in bile-duct-cannulated (BDC) rats. Following repeat oral administration in the rat and dog, increases in systemic exposure to GSK3640254 was generally sub-proportional with dose. There was no or minimal accumulation of GSK3640254 after repeat dosing, and no consistent indication of a difference in exposure between genders.

Metabolic pathways observed in vitro included mono-oxidation, N-dealkylation and direct glucuronidation, with no unique metabolites generated in human liver microsomes or hepatocytes. In rat and dog plasma, GSK3640254 was either the only or the predominant drug-related component with minor oxidative metabolites.

Based on the predicted systemic exposures in human, there is a potential risk for GSK3640254 to act as a perpetrator of drug-drug interactions of substrates of OATP1B3 and MRP2. GSK3640254 was an inhibitor of UGT1A1 and clinical drug-drug interactions via this mechanism could be possible.

Toxicology

The primary target organ of toxicity in non-clinical studies with GSK3640254 was the stomach, with microscopic changes affecting parietal and chief cells in both rats and dogs. Due to microscopic changes in the stomach of rats at the lowest dose tested after 26 weeks, a no observed adverse effect level (NOAEL) in rats was unable to be determined. Microscopic findings in the stomach of rats were minimal to mild at the lowest observed adverse effect level (LOAEL) of 10 mg/kg/day (AUC = 18.9 ug.hr/mL), corresponding to 0.63-fold the measured highest mean human exposure in the planned Phase 2b clinical trial. Following 39-weeks of dosing in dogs, the NOAEL for microscopic changes in the stomach was 0.2 mg/kg/day, and exposures were 0.28-fold the highest clinical exposure. Microscopic stomach changes were associated with increases in serum gastrin when evaluated in the 26- and 39-week studies in rats and dogs, respectively. All microscopic findings in the stomach of rats and dogs and changes in serum gastrin were shown to be reversible following a 4-week recovery period. Microscopic findings in the stomach were minimal to mild at the LOAELs of 10 mg/kg/day (AUC = 18.9 ug.hr/mL) and 1 mg/kg/day (AUC = 46.4 ug/hr/mL) in rats and dogs, respectively, corresponding to 0.63-fold and 1.6-fold highest clinical exposure

in the planned Phase 2b clinical trial. Potential effects in the stomach of humans during clinical trials are being investigated in a gastric safety substudy.

With correction for protein binding, compared to the IC_{50} for the hERG/IKr potassium channel, there is a 15.8-fold margin above the predicted average clinical maximum observed concentration (C_{max}) exposure for the highest dose planned in the study. Exposure where a minimal increase in QT interval was seen in a single dog in the single-dose safety pharmacology study in telemeterized dogs was 3.6-fold higher than the predicted C_{max} at the highest planned dose in the Phase 2a study. In addition, there were no effects on electrocardiogram (ECG) parameters in dogs given up to 25 mg/kg/day for 4 weeks at 19.3-fold above the predicted average C_{max} at the highest dose in the proposed study.

2.2.3. Key Clinical Data on GSK3640254 to date

A summary of safety data from the completed clinical studies performed to date is succinctly described here for convenience.

- No deaths or treatment-related SAEs have been reported during clinical studies with GSK3640254.
- Treatment-related dermatologic AEs (including AEs leading to study discontinuation) included rash, drug eruption, pruritis, urticaria, and maculopapular rash (3 in total: two Grade 1 and one Grade 2 [in study 208132]). AEs of uticaria and maculopapular rash (2 Grade 1: one in study 207187 and one in study 213567) led to discontinuation.
- Treatment emergent drug-related Grade 2-4 AEs included: 1) Headache (2 participants both Grade 2; one participant in Studies 207187 and 208132, each), 2) Nausea (2 participants both Grade 2; one participant in Studies 208134 and 208132, each), and Abdominal Pain (1 participant with Grade 2 AE in Study 208132).
- Clinically notable AEs of elevated transaminases occurred in Studies 207187 (SAD/MAD, n = 1 healthy volunteer) and 208135 (DDI with oral contraceptive Portia [Ethinyl Estradiol and Levongestrel], n = 8 healthy volunteers with elevated transaminases, 5 of which were reported as AEs). Subsequent analysis in Study 208135 showed no PK/PD relationship with either GSK3640254 or Portia and elevated transaminases. The elevated transaminases were likely due to the recent initiation of hormonal contraception in study participants.
- Treatment-related AEs reported in more than 1 study included headache (Studies 207187, 208131, 208135 and 208132) diarrhea (Studies 208132, 207187, 213567 and 208135), nausea (Studies 207187 and 208132) and maculo-papular rash (Studies 208132, 207187 and 213567) abdominal pain (Studies 207187 and 208132).
- Across studies, low grade GI intolerability has been observed: the majority of AEs were mild. Both Studies 207187 (MAD) and 208312 (POC) are relevant to this study given dosing of 7-14 days; most AEs in 207187 were unrelated and most AEs in 208132 were related.
- Across studies, there were generally no clinically significant changes in vital sign measurements, ECG results, or safety laboratory parameters (other than the elevated

transaminases due to Portia, noted above). Specifically, no participant has demonstrated QT prolongation: absolute value >500 msec, or increase from baseline >60 msec.

A comprehensive description of other clinical data of GSK3640254 can be found in Section 5 of the Investigator Brochure and the supporting Clinical Study Reports (available upon request).

2.2.4. Key Phase 2a (Study 208132) Clinical Data on GSK3640254

Study Design and Rationale for Amendment to Shorten Monotherapy in Part 2

Study 208132 was a two-part, Phase 2a, global, multicenter, randomized, partially-blind (Sponsor unblinded), placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability and PK/ PD of GSK3640254 in ART-naïve HIV-1 infected adults. Part 1 evaluated placebo (n=2 participants) and two active doses (10 and 200 mg QD) of GSK3640254 in two dose arms (n=6 participants in each dose arm) – all given for 10 days. Due to the mitigation of treatment emergent A364A/V and A364V genotypic changes seen in the 200 mg arm (described below), Part 2 evaluated placebo (n=2 participants) and three active doses (40, 80, and 140 mg QD) of GSK3640254 in three dose arms (n=6 participants in each dose arm) – only given for 7 days.

Primary Objective: Antiviral decline after 7 to 10 days of monotherapy

Of the 34 randomized participants in Part 1 and 2 combined, the average age was 32 years. Two females were randomized. The short-term antiviral response is shown in Table 1.

Table 1 Summary of Plasma HIV-1 RNA (log 10 c/mL) Change from Baseline and Maximum Decline from Baseline in 208132

	GSK3640254					Placebo	
	10 mg Part 1	40 mg Part 2	80 mg Part 2	140 mg Part 2	200 mg Part 1	Part 1	Part 2
	N = 6	N = 6	N = 6	N = 6	N = 6	N = 2	N = 2
Baseline							
Mean	4.187	4.672	4.433	4.533	4.820	4.245	4.750
Median	4.180	4.690	4.255	4.455	4.825	4.245	4.750
Change from Baseline at Day 8, 9, or 10 (Part 1) or Day 8 (Part 2)							
Mean	-0.137	-1.178	-1.015	-1.450	-1.700	0.155	0.150
Median	-0.125	-1.145	-1.035	-1.410	-1.570	0.155	0.150
SD	0.3730	0.4358	0.3299	0.2353	0.3447	0.0354	0.2263
Maximum Change from Baseline within Study Period							
Mean	-0.363	-1.178	-1.015	-1.488	-2.013	-0.205	-0.030
Median	-0.280	-1.145	-1.035	-1.445	-1.960	-0.205	-0.030
SD	0.2519	0.4358	0.3299	0.2671	0.3292	0.2616	0.1273

Secondary Objective: Assessment of Safety/Tolerability

There were no deaths. There were two SAEs: 1) unrelated severe dilated congestive cardiomyopathy (Grade 3), and 2) anal abscess (Grade 1). The participant with unrelated severe dilated congestive cardiomyopathy also had an AE of unrelated idiopathic myocarditis (Grade 3). Both SAEs and the AE were unrelated to study medication. Note, the participant with congestive cardiomyopathy received GSK3640254 10 mg. An in-depth discussion of this participant's clinical course is location in Section 5.3.2.5. of the IB.

There were no AEs which led to discontinuation. There were 9 participants with 14 related AEs. Of these 14, 11 were Grade 1 (mostly gastrointestinal in nature) and three were Grade 2 (rash maculo-papular, abdominal pain and nausea).

Of the 34 participants randomized, 22 participants developed 50 individual AEs. There were 7 participants with seven Grade 2 AEs: abdominal pain (related), nausea (related), pyrexia, spine pain, rash maculo-papular (related), headache, and neutropenia. The remaining AEs are shown in Table 2. The most frequent AEs occurred in the Infections/Infestations SOC (8 participants). The most frequent individual AE was headache (4 participants). Although not shown, all GI AEs and Neuro AEs were less than 1 day in duration except: 1) one participant had a headache (Grade 1) from Study Day 1-2, 2) one participant had diarrhea and vomiting (both Grade 1) from Study Day 4-9, and 3) one participant had constipation (Grade 1) from Study Day 1-5.

Table 2 Summary of All Adverse Events by Preferred Term (Safety Population)

Preferred Term	GSK 10 mg (N=6)	GSK 40 mg (N=6)	GSK 80 mg (N=6)	GSK 140 mg (N=6)	GSK 200 mg (N=6)	Placebo (N=4)	Total (N=34)
Any Event	**3 (50)**	**5 (83)**	**4 (67)**	**5 (83)**	**5 (83)**	**0**	**22 (65)**
Headache	0	1 (17)	0	1 (17)	2 (33)	0	4 (12)
Diarrhoea	1 (17)	1 (17)	0	0	1 (17)	0	3 (9)
Oropharyngeal pain	0	0	0	1 (17)	2 (33)	0	3 (9)
Nasopharyngitis	0	0	0	0	2 (33)	0	2 (6)
Vomiting	1 (17)	0	0	0	1 (17)	0	2 (6)
Abdominal pain	0	0	2 (33)	0	0	0	2 (6)
Lymphadenopathy	1 (17)	0	0	0	1 (17)	0	2 (6)
Anal abscess	0	0	0	1 (17)	0	0	1 (3)
Meningococcal infection	1 (17)	0	0	0	0	0	1 (3)
Pharyngitis	0	0	0	0	1 (17)	0	1 (3)
Upper respiratory tract infection	0	0	0	0	1 (17)	0	1 (3)
Urinary tract infection	0	0	0	1 (17)	0	0	1 (3)
Viral infection	0	1 (17)	0	0	0	0	1 (3)
Constipation	0	0	0	1 (17)	0	0	1 (3)

Preferred Term	GSK 10 mg (N=6)	GSK 40 mg (N=6)	GSK 80 mg (N=6)	GSK 140 mg (N=6)	GSK 200 mg (N=6)	Placebo (N=4)	Total (N=34)
Nausea	1 (17)	0	0	0	0	0	1 (3)
Migraine	0	0	1 (17)	0	0	0	1 (3)
Presyncope	0	1 (17)	0	0	0	0	1 (3)
Asthenia	0	0	0	0	1 (17)	0	1 (3)
Fatigue	0	1 (17)	0	0	0	0	1 (3)
Nodule	0	0	1 (17)	0	0	0	1 (3)
Pyrexia	0	0	0	0	1 (17)	0	1 (3)
Catarrh	0	0	0	0	1 (17)	0	1 (3)
Epistaxis	0	1 (17)	0	0	0	0	1 (3)
Neutropenia	0	0	1 (17)	0	0	0	1 (3)
Pain in extremity	0	0	1 (17)	0	0	0	1 (3)
Spinal pain	1 (17)	0	0	0	0	0	1 (3)
Dermatitis atopic	0	0	1 (17)	0	0	0	1 (3)
Pruritus	0	0	0	1 (17)	0	0	1 (3)
Rash maculo-papular	0	0	0	1 (17)	0	0	1 (3)
Congestive cardiomyopathy	1 (17)	0	0	0	0	0	1 (3)
Myocarditis	1 (17)	0	0	0	0	0	1 (3)
ALT increased	1 (17)	0	0	0	0	0	1 (3)
AST increased	1 (17)	0	0	0	0	0	1 (3)
Hyperglycaemia	1 (17)	0	0	0	0	0	1 (3)
Insulin resistance	1 (17)	0	0	0	0	0	1 (3)
Vitamin D deficiency	1 (17)	0	0	0	0	0	1 (3)
Chromaturia	1 (17)	0	0	0	0	0	1 (3)

Source Data: Table 3.2 of CPSR 208132

There were no abnormal clinically significant arrhythmias or corrected QT interval (QTc) prolongations (values >500 msec or increases >60 msec from baseline) observed for any participant. There were no clinically significant trends in vital signs, chemistry laboratory values, or hematology laboratory values across the arms.

CCI

[redacted]

CCI

[redacted]

Secondary Objective: Characterization of PK Profile

GSK3640254 PK parameters derived based on nominal times following once-daily administration of 10 mg and 200 mg once daily for 10 days were determined on Day 1 (Part 1 and 2) and either Day 8-9 (Part 1) or Day 7 (Part 2) (Table 3). Following once-daily administration of GSK3640254 over 10 mg to 200 mg dose range with a moderate fat meal, Day 1 median T_{max} ranged between 3.00 – 5.5 hours. Variability in the PK parameters [% between-participant coefficient of variation (CVb)] ranged from 19% to 52%.

Steady-state (Day 8-9 or 7 for Part 1 and Part 2, respectively) median T_{max} ranged between 4.00 h and 5.50 h. Variability in the PK parameters [%CVb] was low to moderate, ranging from 19.5% to 47%.

Although the sample size is small, GSK3640254 demonstrated generally dose-proportional PK over the dose range studied (10 – 200 mg). Consistent with antiviral decline described above, the PK parameters of: a) 40 and 80 mg approximated each other, and b) 140 and 200 mg approximated each other. There were three participants in the 80 mg arm who had exposure similar to that observed at 40 mg dose (data not shown).

Table 3 Summary Statistics of Day 1 and Day 8-9 (Part 1) or Day 7 (Part 2) PK Parameters Following Multiple Daily Dose Administration of GSK3640254 in Study 208132

		10 mg n=6	40 mg n=6	80 mg n=6	140 mg n=6	200 mg n=6[1]
	PK Parameter	Geometric Mean [CVb%] (95% CI)				
Day 1	AUC(0-24) (µg*h/mL)	0.695 [13.5] (0.588, 0.821)	3.25 [31.7] (2.35, 4.50)	6.12 [38.8] (4.13, 9.07)	14.0 [36.6] (9.67, 20.4)	12.4 [91.3] (5.48, 28.0)
	Cmax (µg/mL)	0.059 [177.4] (0.017, 0.207)	0.232 [30.5] (0.169, 0.317)	0.433 [33.6] (0.307, 0.610)	0.918 [41.5] (0.604, 1.395)	0.938 [82.3] (0.441, 2.00)
	Tmax (h) (median)[range]	2.93 [0.00, 5.00]	4.42 [3.97, 8.00]	4.08 [2.95, 6.17]	5.51 [3.00, 6.25]	5.53 [3.92, 8.05]
Steady State [2]	AUC(0-24) (µg*h/mL)	0.908 [44.7] (0.580, 1.422)	7.46 [26.8] (5.66, 9.84)	11.8 [26.7] (8.98, 15.6)	29.3 [27.9] (22.0, 39.0)	27.9 [18.4] (23.1, 33.8)
	Cmax (µg/mL)	0.055 [41.3] (0.036, 0.083)	0.469 [20.6] (0.379, 0.581)	0.747 [23.7] (0.585, 0.955)	1.86 [26.0] (1.42, 2.43)	1.86 [19.5] (1.51, 2.27)
	Tmax (h) (median)[range]	4.02 [1.87, 5.00]	4.06 [2.00, 8.00]	4.58 [4.00, 5.18]	4.08 [2.92, 5.20]	5.48 [3.00, 6.20]
	Ctau (µg/mL)	0.027 [47.0] (0.017, 0.043)	0.219 [30.1]	0.360 [31.1]	0.798 [34.1]	0.703 [29.6]

		10 mg n=6	40 mg n=6	80 mg n=6	140 mg n=6	200 mg n=6[1]
	PK Parameter	**Geometric Mean [CVb%] (95% CI)**				
			(0.161, 0.298)	(0.262, 0.495)	(0.563, 1.131)	(0.519, 0.953)

CI = Confidence interval
[1]One participant In the 200 mg group has been excluded from PK analysis for day 1 due to vomiting within 1x tmax post-dose
[2]Steady State was measured at Visit 5/6 (Day 8/9 in Part 1 vs Day 7 in Part 2) [Based on FTIH study, mean half-life ranges between 21h – 28h]

The key PK modelling and simulation data from Study 208132 is summarized in the dose justification in Section 4.3.

2.3. Benefit/Risk Assessment

Based upon preclinical and clinical studies (including the prior MI GSK3532795), the potential risks for GSK3640254 are GI intolerability (e.g., abdominal pain and diarrhea) and gastric toxicity (effects on parietal cell and chief cells), prolongation of the corrected QT interval (QTc), neuropsychiatric safety, skin and subcutaneous tissue disorders, and treatment emergent virologic resistance.

First, GI intolerability and gastric toxicity (e.g., single-cell parietal cell necrosis) will be assessed using clinical and invasive monitoring as outlined in Section 1.3 and Section 8.6.1.

Second, prolongation of the QTc interval is a risk. One preclinical study showed 1 dog with an increased QTc interval when given a single dose of GSK3640254. A cardiodynamic analysis of healthy participants in Study 207187 was conducted. A final model from the MAD data showed a QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses (administered with a moderate fat meal), respectively, on Day 14 (the top two doses in the trial). Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately 200 mg QD; note, 200 mg QD is the top dose considered for this Phase 2b study). Importantly, in GSK3640254 clinical trials to date, there have been no abnormal clinically significant arrhythmias, and no participants met the trial based QTc stopping criteria for QTcF prolongations: values >500 ms or increases >60 ms from Baseline. This study contains specific cardiac exclusion criteria, has ECG monitoring (at T_{max} once GSK3640254 attains steady state concentration), and has QTcF based stopping criteria (See Section 1.3, Section 5.2, and Section 7.1.4).

Third, given the risk of psychiatric risks seen with GSK3532795 (see Section 2.3.1) the protocol will exclude potential participants with any significant pre-existing psychiatric condition including the results of an assessment using the Columbia Suicide Severity Rating Scale (C-SSRS). Participants will also be required to provide response to the C-

SSRS during the on-treatment portion of the study – and will be clinically evaluated for suicidality as indicated (See Section 1.3, Section 5.2 and Section 8.2.6).

Fourth, across clinical trials in HIV-1 infected participants and healthy participants, skin and subcutaneous tissue disorders have been observed (in some cases leading to discontinuation). Participants will be followed regularly for the development of AEs and will undergo physical exams throughout the study.

Last, the risk of treatment emergent resistance (to any ARV) will be addressed by several means. First, a HIV-1 RNA at Week 2 will be obtained to demonstrate a decline relative to Day 1. Second, the following resistance assays will be obtained from Monogram on Day 1 and Week 4 samples from all participants in the GSK3640254 treatment arms: Gag genotype (using a Next Generation Sequencing Platform), PhenoSense Gag Assay for GSK3640254, PhenoSense GT, GeneSeq Integrase and PhenoSense Integrase. These assays will document the emergence of resistance or decreased susceptibility in advance of protocol-defined virologic failure (PDVF) – thereby preserving as many ARV options for participants. Additionally, participants (in all treatment groups) will have their HIV-1 RNA monitored at frequent intervals and have criteria for resistance testing based upon the development of PDVF (Section 1.3 and Section 7.1.1).

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability/reversible gastric toxicity, QTc prolongation, skin and subcutaneous tissue disorders, and neuropsychiatric safety), this clinical study will include relatively healthy HIV-1 infected treatment-naïve adults who will receive clinical, ECG, and laboratory evaluations during their participation.

This study includes an optional Stomach Substudy that includes the procedure of an EGD with biopsy. The procedural risks and mitigation are outlined in Section 2.3.1.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK3640254 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2018N379610_02].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Non-clinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with complementary DNA from the ion channels. In a single-dose safety pharmacology study in telemeterized dogs, increases in QT interval (up to 20 ms) occurred primarily in 1 dog given 17 mg/kg. Later, there were no GSK3640254-related effects on electrocardiogram (ECG) parameters in dogs given up to 25 mg/kg/day for up to 39 weeks. In Study 207187 (MAD) the concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately 200 mg QD). Importantly, in GSK3640254 clinical trials to date, there have been no abnormal clinically significant arrhythmias, and no participants have met the trial-based Stopping Criteria for QTcF prolongations: values >500 ms or increases >60 ms from Baseline.	Protocol exclusion criteria based on screening ECG parameters and cardiac medical history (see Section 5.2). Participants will have regular ECG monitoring during the course of the study (see Section 1.3) with QTc stopping criteria (see Section 7.1.4). As noted in Section 7.1.4, if a clinically significant finding is identified (including but not limited to changes from baseline in QT interval corrected using or Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant meets QTc Stopping Criteria, and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported (at a minimum) as an AE.
Gastrointestinal intolerability	Non-clinically, signs of gastrointestinal intolerability (sporadic vomiting and abnormal faeces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. In humans, GI	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms (see Section 5.2)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	intolerability (predominately abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was evaluated through Phase 2b dosing. While summarized in detail in the IB, the rates of all GI AEs (all Grade 1 regardless of relationship) in the MAD portion of Study 207187 (Phase 1 FTIH) were 33%, 0%, 24%, and 29% in participants who received GSK3640254 50, 100, 200, and 320 mg daily for 14 days (the only completed study with the greatest duration and dose of dosing), respectively (relative to a rate of 21% in participants who received placebo). The rates of all GI AEs in Study 208132 (Phase 2a POC) study are shown in Section 2.2.4.	Participants will undergo continuous evaluation for adverse events during their participation in the trial; there are clinical stopping criteria based upon intensity of treatment-emergent AEs (see Section 7.1). Additionally, a GI intolerability evaluation and monitoring plan is available to guide the investigator should GI AEs emerge (see Section 8.2.7)
Gastric Toxicity	Gastric toxicity effects on parietal cells and/or chief cells associated with changes in serum gastrin levels were present in preclinical species. These findings were reversible.	It is unclear if gastric toxicity occurs in humans; and if present what the histopathological findings are (whether they correlate with AEs, biomarkers, etc). To explore the monitoring of gastric toxicity, a subset of ~7 participants in each arm will take part in the Optional Stomach Substudy and will undergo [CCI] with Biopsy of the greater and lesser curvature (for subsequent histopathologic examination) along with a measurement of Serum Biomarkers (See Section 1.3 and Section 8.6.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		Individual and Protocol based discontinuation criteria will be based upon treatment emergent histologic findings (see Section 4.1.5.2 and Section 4.1.5.3).
Neurologic/psychiatric safety	Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in a TQT study. From a Neurologic and Psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies, mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. While summarized in the IB, the rates of all Nervous system and Psychiatric AEs in the MAD (Study 207187 FTIH) ranged from 24-57% and 0-17%, respectively across doses (50-320 mg x 14 days) without any trend. No GSK3640254 clinical trial has observed SAEs of acute psychosis or homicidal/suicidal ideation.	Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment and the eCSSRS tool) in participants. Continuous evaluation for adverse events during their participation in the trial including direct AE inquiry as noted in Section 1.3. Participants will also provide responses to the C-SSRS throughout the study. Ultimately, in the event of a new onset suicidality ideation or behavior (SIB), as determined by the investigator (in consultation with psychiatry, as needed), the participant will discontinue from the trial and the Investigator will arrange for urgent specialist psychiatric evaluation and management. Guidance for the management of emergent psychiatric symptoms are available (see Section 8.2.6).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		There are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 7.1).
Skin and subcutaneous tissue disorders	Across clinical trials, AEs leading to discontinuation have included urticaria and maculo-papular rash	Participants with a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation are excluded. Participants will undergo continuous evaluation for adverse events during their participation in the trial supplemented by the use of physical exams. Protocol includes individual participant stopping criteria, including any Grade 3 or higher rash, or Grade 2 rash that is associated with any systemic signs, allergic symptoms or if mucosal involvement develops. (see Section 10.9.3).
ABC		
Hypersensitivity Reaction	Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir. Participants who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele.	Testing for the HLA-B*5701 allele will be done at Screening so that Investigators can make an appropriate choice among the study background therapy options. Guidelines for the management of HSR are provided in Section 10.9.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	Both ABC and DTG are associated with a risk for hypersensitivity reactions (HSR) and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement.	Also see Section 7.1, Discontinuation of Study Intervention. The participant informed consent form (ICF) includes information on this risk and the actions participants should take in the event of an HSR or associated signs and symptoms
DTG		
Hypersensitivity reaction (HSR) and rash	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 drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation, are excluded. Guidelines for the management of HSR are provided in Section 10.9.2. Also see Section 7.1, Discontinuation of Study Intervention. Specific/detailed toxicity management guidance is provided for rash (Section 10.9.3.1) The participant informed consent form (ICF) includes information on this risk and the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		actions participants should take in the event of a HSR or associated signs and symptoms.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	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) ≥3 times the-upper limit of normal (ULN) or ALT ≥2xULN and bilirubin ≥1.5x ULN • Infection with Hepatitis B or Hepatitis C, as described in the Exclusion Criteria (See Section 5.2) Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 10.9.1).
Psychiatric disorders	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.	Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment and the eCSSRS tool) in participants.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		Continuous evaluation for adverse events during their participation in the trial including direct AE inquiry as noted in Section 1.3. Participants will also provide responses to the C-SSRS throughout the study. Ultimately, in the event of a new onset suicidality ideation or behavior (SIB), as determined by the investigator (in consultation with psychiatry, as needed), the participant will discontinue from the trial and the Investigator will arrange for urgent specialist psychiatric evaluation and management. Guidance for the management of emergent psychiatric symptoms are available (see Section 8.2.6). There are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 7.1). The participant informed consent form includes information on the risk of depression and suicidal ideation and behavior.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 6.8.1).
Renal function	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.	Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 10.9.6). 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.
Neural tube defects	In a birth outcome surveillance study in Botswana there have been 7 cases of neural tube defects reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens from the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens from the time of conception (Prevalence Difference 0.09%; 95% CI 0.03-0.30). In the same study, no increased risk of neural tube defects was reported in women who started DTG during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748	1. Participants who are female at birth who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 2. Participants who are female at birth 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. 3. Participants of reproductive potential are reminded re: pregnancy avoidance and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy. Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir. More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes. In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified. Dolutegravir was shown to cross the placenta in animals.	adherence to contraception requirements at every study visit. 4. Pregnancy status is monitored at every study visit

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
FTC/TAF		
New onset or worsening renal impairment	Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials.	Guidelines for monitoring are provided in Appendix 9, Toxicity Management (specifically, Section 10.9.6)
Proximal Renal Tubule Dysfunction	In clinical trials of FTC+TAF with EVG+COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC+TAF with EVG+COBI with estimated creatinine clearance greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI. In a study of virally suppressed subjects with baseline estimated creatinine clearance between 30 and 69 mL per minute treated with FTC+TAF with EVG+COBI for a median duration of 43 weeks, FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline estimated creatinine clearance between 30 and 50 mL per minute	Guidelines for monitoring are provided in Appendix 9, Toxicity Management (specifically, Section 10.9.7)
Proteinuria	Prior to or when initiating DESCOVY, and during treatment with DESCOVY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine	Guidelines for monitoring are provided in Appendix 9, Toxicity Management (specifically, Section 10.9.8)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	clearance, urine glucose, and urine protein in all individuals	
Study Procedures		
Optional EGD with biopsy	The overall complication rates for EGD range from 0.009% to 1.9%.% [Wolfsen, 2010]. The mortality rate ranges from 0 – 0.05% [Ben-Menachem, 2012]. Risks associated with an EGD with biopsy include hypoxia, cardiovascular complications 0.14%- 0.9% (e.g. hypotension, shock, supraventricular tachycardia, vasovagal reaction, myocardial infarction, cerebrovascular accidents), aspiration, pneumonia, apnea, respiratory arrest, a reaction to medication (e.g. methemoglobinemia), infection (0-8%) [Ben-Menachem, 2012], bleeding (0.15%), incarceration, and/or perforation (0.02-0.2%).	Only qualified medical professionals with appropriate supportive staff/environment will evaluate potential participants, perform the procedure, and provide post-procedure care. Additional requirements are detailed in Section 4.1.5.
HIV-1 Infection/Patient Population		
HIV Resistance to GSK3640254 and other on-study treatments	There is an in intrinsic risk of resistance (genotypic changes or decreased phenotypic susceptibility) to any developmental ARV (or the ARVs which are co-administered). Note: Data from Study 208132 (Phase 2a POC) showed a decline in HIV-1 RNA and reasonable PK profile. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on or after Day 11 (after 10	As described above, this risk will be mitigated using the following approaches. 1) HIV-1 RNA at Week 2 will be obtained to demonstrate a decline relative to Day 1. 2) At Day 1 and Week 4 the following resistance assays will be obtained from Monogram Biosciences on samples collected from participants in the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	days of receiving GSK3640254 monotherapy). However, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed as there is no known cross-resistance between maturation inhibitors and other classes of ARVs.	GSK3640254 arms: Gag genotype (using a Next Generation Sequencing Platform), PhenoSense Gag Assay for GSK3640254, and PhenoSense GT, GeneSeq Integrase and PhenoSense Integrase. These assays will document the emergence of resistance or decreased susceptibility in advance of PDVF – thereby preserving as many ARV options for participants. 3) All participants will have their HIV-1 RNA monitored at frequent intervals and have criteria for resistance testing based upon the development of Protocol Defined Virologic Failure (Section 7.1.1)

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.

2.3.2. Benefit Assessment

Participants in this clinical study may benefit from receiving a combination of ARVs containing GSK3640254. Data from the Phase 2a study does show a PK/PD (decline in HIV-1 RNA) relationship (described in detail in Section 4.3). Thus, GSK3640254 may contribute to a decline in HIV-1 RNA (and maintenance of suppression) when administered with other ARVs. A decline in HIV-1 RNA is directly associated with a reduction in HIV/AIDS related morbidity/mortality.

There is no clinical benefit to participating in the optional Stomach substudy.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize the potential risks to participants in this study, the potential risks identified in association with GSK3640254 are justified by the anticipated benefits that may be afforded to participants with HIV-1 infection achieving and maintaining virologic suppression (when given in combination with other ARVs).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy	
• To evaluate antiviral efficacy of GSK3640254 relative to DTG, each given in combination with 2 NRTIs, enabling the selection of an optimal dose for GSK3640254	• Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24 using the FDA snapshot algorithm
Secondary Efficacy, Safety and PK	
• To evaluate antiviral efficacy in the Randomised Phase of GSK3640254 relative to DTG, each given in combination with 2 NRTIs at Week 48 • To evaluate antiviral efficacy in the Non-Randomised Phase of GSK3640254 optimal dose given in combination with DTG relative to the reference arm (DTG given in combination with 2 NRTIs) at Week 96	• Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Weeks 48 and 96 using the FDA snapshot algorithm • Absolute values and changes from baseline in HIV-1 RNA through Weeks 24, 48, and 96 • Absolute values and changes from baseline in CD4+ cell counts through Weeks 24, 48, and 96
• To evaluate safety and tolerability in the Randomised Phase of GSK3640254 relative to DTG each given in combination with 2 NRTIs at Weeks 24 and 48 • To evaluate safety and tolerability in the Non-Randomised Phase of GSK3640254 optimal dose given in combination with	• Frequency of SAEs, Deaths and AEs leading to Discontinuation through Weeks 24, 48, and 96 • Incidence and severity of AEs through Weeks 24, 48 and 96

Objectives	Endpoints
DTG relative to the reference arm (DTG given in combination with 2 NRTIs) at Week 96	• AEs in GI, Psych/CNS through Weeks 24, 48, and 96
• To assess the development of viral resistance in the Randomised Phase to GSK3640254 and 2 NRTI backbone in participants experiencing virologic failure at Weeks 24 and 48. • To assess the development of viral resistance in the Non-Randomised Phase to GSK3640254 and DTG in participants experiencing virologic failure at Week 96.	• Changes in genotypic and/or phenotypic profiles of virus compared to baseline through Weeks 24, 48, and 96
• To characterize the pharmacokinetics of GSK3640254 when given in combination with ABC/3TC or FTC/TAF	• The steady-state plasma PK parameters of GSK3640254 will be assessed based on Intensive and/or Sparse PK sampling through Weeks 24 and 48
CCI [redacted]	

CCI

[redacted]

4. STUDY DESIGN

4.1. Overall Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities table (Section 1.3), are essential and required for study conduct.

Study 208379 is a Phase 2b, randomized, multicentre, parallel group, partially-blind (only to the doses of GSK3640254) trial, to be conducted in approximately 150 HIV-1 infected ART-naïve adults.

Independent Data Monitoring Committee:

The study will include an Independent Data Monitoring Committee (IDMC).

The IDMC will review the totality of clinical data (exclusive of the Stomach Substudy) with at least one analysis before the Week 24 Primary Analysis and will be responsible for recommending to the CMO and VSLC: 1) discontinuation of any treatment arm, 2) discontinuation of the study, or 3) continuation of the study as planned.

4.1.1. Screening Period

Assuming a screen failure rate of 50%, approximately 300 participants will be screened for this study to randomize approximately 150 eligible participants.

The enrollment period may be extended if the additional effort is needed to recruit additional participants for the optional Stomach Substudy (see Section 4.1.5.1).

Participants will enter a Screening period of up to 42 days. This duration is warranted based on the lengthy turnaround time for the central geno/phenotypic assay from Monogram. The Screening period (delaying Randomization) may be extended to a maximum of 63 days in certain circumstances, as detailed in Section 5.5.

At the Screening visit, fasting blood samples and urine will be collected, an ECG will be done, and participants will be asked to provide responses to the C-SSRS Baseline assessment about thoughts and feelings throughout their entire lifetime. In addition, participants will provide breath or stool samples for the testing of *H. pylori,* to be done at

a lab that is local to the study site. The local laboratory should be consulted prior to study start for any pre-testing requirements.

Prohibited Medications (Section 6.8.1.2) will be reviewed for any medications the participant is taking that need to be stopped as much as 4 weeks prior to the first dose.

Participants may be rescreened once (See Section 5.4). However, participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be rescreened.

4.1.1.1. Selection of NRTI Background Therapy: ABC/3TC of FTC/TAF

The Investigator will select the ABC/3TC or FTC/TAF NRTI background therapy for each participant.

- The selection of the fixed-dose combination NRTI backbone should be based on subject history and current medical conditions. In countries where the therapy is not provided centrally, Investigators must refer to local product labeling and treatment guidelines for these products.
- Results for the *HLA-B*5701* allele testing will help inform the decision. The use of ABC/3TC is contraindicated for those who carry the allele.
- The use of the ABC/3TC NRTI backbone is contraindicated in subjects with mild hepatic impairment (Child-Pugh score 5-6, Class A) [Epzicom USPI, 2019].

4.1.2. Treatment Period

Visits, in clinic or virtual, may be conducted within a window of ± 2 days.

The Week 2 visit must be done from Day 11-14.

Any interruption in therapy during the treatment period of 3 or more consecutive days, for any reason, must be discussed with the ViiV Medical Monitor prior to resumption of .therapy, if possible. If therapy was resumed without prior approval (i.e., if the PI was not aware at the time of the missed doses), the Investigator should contact the ViiV Medical Monitor upon becoming aware.

Participants will be asked to complete a diary card for at least a portion of the study that will capture key dosing times prior to visits that collect PK samples as well as dates of any missed doses that can be recalled. Site staff will perform pill counts to check compliance. At every visit, both in clinic and virtual, site staff will discuss the importance of adherence, ensuring participants understand the risk for developing resistance that comes with non-compliance.

Dose administration on all arms requires participants to dose in the morning (at least through Week 48, due to study PK and/or post-dose ECG requirements and for consistency of daily dosing), and at/near the same time each day (see the SRM for guidance).

Dose administration with the treatments in the GSK3640254 arms requires participants to dose with a low-fat meal (see Section 5.3.1). Dose administration with DTG can be done without regard to food.

All subjects in the GSK3640254 arms will provide samples for Sparse PK at visit Weeks 4, 8, 12, 24, 36 and 48. At each of these visits, a PK sample is drawn at the beginning of the visits, pre-dose, with all of the other blood samples, and then within a window of time later that same day, a second PK sample is drawn. Some visits (See Section 8.4) will require the second PK sample to be collected much later in the day, requiring the subject to return to the clinic. Subjects in the Reference Arm will not need to provide samples for PK.

The Week 2 visit will be conducted Day 11-14. The reason for this is two-fold: it allows sufficient time for the study drugs to come to steady state for those participating in the Intensive PK portion of this visit (see Section 4.1.2.1.1) and it also represents a sufficient length of time to see any effect of early decline in HIV RNA.

The visit at Week 2 is to be done by all study participants (for collection of HIV-1 RNA, plasma for storage, a pre-dose ECG and all 3 post-dose ECGs). Participants on the GSK3640254 arms can volunteer to take part in the Intensive PK portion at Week 2 (~45 volunteers from the GSK3640254 arms are needed; approximately 15 per arm). Subjects in the Reference Arm will not do the Intensive PK portion of the visit at Week 2.

Fasting requirements:

- Participants who are taking part in the Stomach Substudy will need to fast for a minimum of 12 hours prior to the visits at which Serum Biomarkers are collected, and for only 6 hours at visits where lipids but not Serum Biomarkers are collected

- All other participants need to fast for a minimum of 6 hours prior to the visits at which lipids and renal/bone/inflammation biomarkers are collected.

4.1.2.1. Day 1 through Week 24

Participants will be randomized to either: one of the three blinded, QD, oral dose GSK3640254 dose regimens (approximately 40 participants per treatment arm, each in combination with open label ABC/3TC or FTC/TAF), or to the open label, active control Reference Arm of DTG given in combination with open label ABC/3TC or FTC/TAF (approximately 30 participants) in the Randomised Phase.

- Arm 1: Blinded GSK3640254 100 mg + Open Label ABC/3TC or FTC/TAF

- Arm 2: Blinded GSK3640254 150 mg + Open Label ABC/3TC or FTC/TAF

- Arm 3: Blinded GSK3640254 200 mg + Open Label ABC/3TC or FTC/TAF

- Arm 4: Open Label DTG + Open Label ABC/3TC or FTC/TAF

On Day 1, there are several pre-dosing assessments and procedures, then ECGs are also required 2, 4 and 6 hours post-dose.

Participants will be stratified by Screening plasma HIV-1 RNA, by <100,000 c/mL or ≥100,000 c/mL, and the investigator's choice of dual NRTI background therapy (either ABC/3TC or FTC/TAF).

A one-time switch to the other option of the NRTI background is permitted prior to Week 2 for reasons of tolerability/toxicity, no other switch will be allowed. The chosen background therapy for each participant will be maintained throughout the entire duration of trial participation.

Participants will be seen in-clinic for study visits every 4 weeks through Week 24.

At these clinic visits, blood and urine will be collected, ECG(s) will be done at some visits, and participants will be asked to provide responses to the C-SSRS *Since Last Visit* questions about their thoughts since the last visit.

4.1.2.1.1. Optional Intensive PK Portion of Week 2 Visit – GSK3640254 Arms Only

The visit at Week 2 is to be done by all study participants, but the Intensive PK portion of the visit is optional, and limited to participants who are on the GSK3640254 arms.

The study includes an Intensive PK portion at the visit at Week 2 ([Day 11-14]; also called the PK Subgroup) to be performed by approximately 45 participants who are assigned to any of the GSK3640254 arms (approximately 15 per treatment arm; 25% of the total). Participation is optional; a sufficient dataset is needed for the analysis of this secondary endpoint.

The Intensive PK portion of the visit includes a standard, pre-dose blood draw in the morning, followed by 8 blood draws of smaller blood volume over the course of the subsequent 6 hours, then another approximately 4 hours later, and then a final, small blood draw the following morning (See Section 8.4). EGCs will be collected at some of the time points.

If, due to COVID-19, the Week 2 visit is impacted (e.g., the participant is restricted by travel or the clinic has restrictions at the time that limit attendance or otherwise prohibit the ability to conduct this day-long visit), then the Intensive PK portion of the visit can be postponed and done at Week 16, in conjunction with the required assessments and procedures required for Visit 16. See the SRM for the management of tests/assessments that would be duplicative and instructions on how to manage the collection using the 2 lab kits and data entry into the eCRF.

4.1.2.2. Week 24 through End of Study

Beyond Week 24, participants will be seen in-clinic for visits approximately every 4 weeks for another 9 months, then approximately every 8 weeks through the remainder of the second year of participation, and then every 12 weeks until the end of the study.

Participant in the DTG reference arm will end their participation in the treatment phase of the study as each individual participant reaches Week 144.

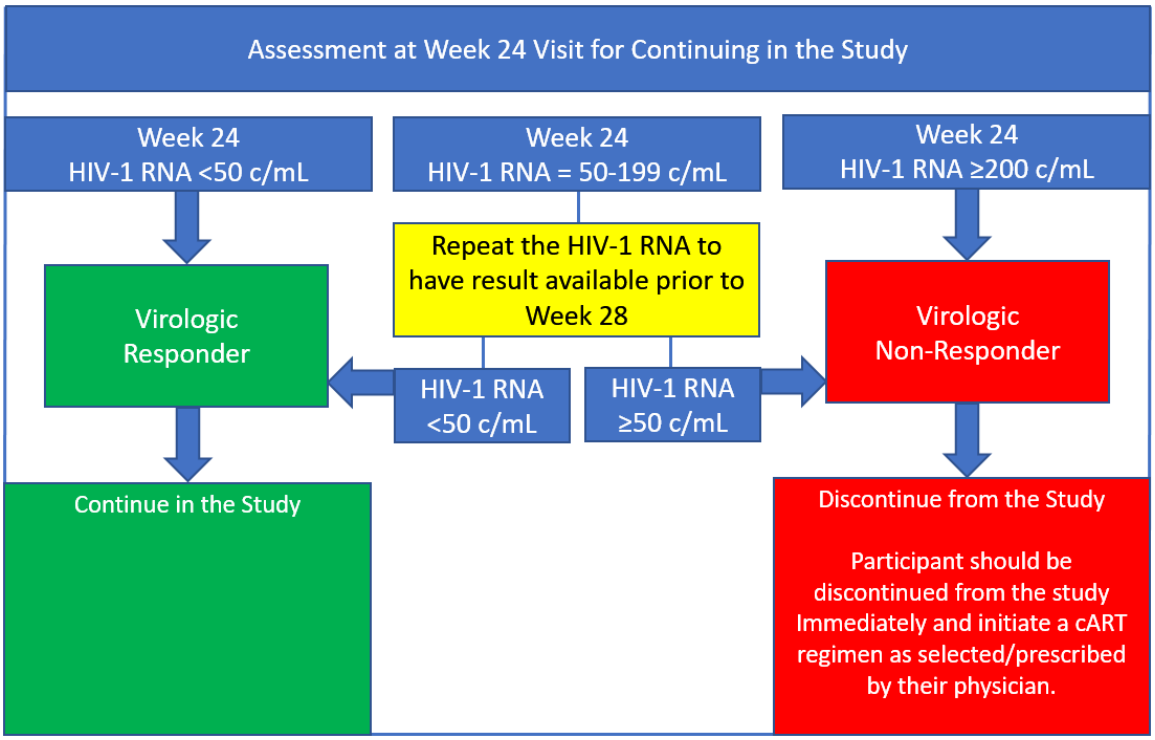
4.1.2.2.1. Virologic Management

See the decision tree in Figure 1.

Participants in any arm who are Virologic Responders will continue in the study beyond Week 24 without change.

Participants in any arm who are Virologic Non-Responders must be discontinued from the study immediately. These participants will perform the Early Withdrawal visit, and then be seen in clinic once more at a Final Follow-Up visit.

Figure 1 Assessment by HIV-1 RNA at Week 24



Refer to Table 4 for management by HIV-1 RNA after all participants in the GSK3640254 arms transition to open label GSK3640254 optimal dose + DTG.

For the purposes of clinical management in this study, Investigators will continuously assess HIV-1 RNA throughout the Treatment Phase of the trial (from Day 1, at any visit either scheduled or unscheduled) using information found in Section 7.1.1 and the guidance as seen in Table 4 (during the Non-Randomized Phase of the study). The rationale for this specific virologic management in the Non-Randomized Phase is the difference in therapy for virologically suppressed participants who will transition to open label GSK3640254 optimal dose + DTG. Specifically, DTG has one of the highest barriers to resistance and participants will need to be closely evaluated in this portion of the study to ensure they do not develop overt resistance to the INI class of medications.

Table 4 Assessment by HIV-1 RNA During the Non-Randomized Phase

Current HIV-1 RNA <50 c/mL	Regardless of previous HIV-1 RNA result, proceed with the next visit, per Schedule of Activities (SOA) in Section 1.3.
Current HIV-1 RNA ≥50 c/mL but <200 c/mL	If previous HIV-1 RNA result was <50 c/mL, perform a scheduled or unscheduled visit to reassess HIV-1 RNA[a] in a time frame consistent with Section 7.1.1.1. If previous HIV-1 RNA result was ≥50 c/mL, discuss results with the ViiV medical monitor[b,c] Participant has met criteria for additional HIV-1 RNA testing or possible withdrawal. If the participant is withdrawn under the above criteria, they will have met "Precautionary Virologic Withdrawal Criteria (PVW)" If the 2 previous consecutive HIV-1 RNA results were ≥50 c/mL and <200 c/mL, the participant has not met PVW.
Current HIV-1 RNA ≥200 c/mL	If previous HIV-1 RNA result was <50 c/mL, perform a scheduled or unscheduled visit to reassess HIV-1 RNA[a] in a time frame consistent with Section 7.1.1.1. Participant has met "Suspected Virologic Withdrawal Criteria (SVW)". • If the repeat HIV-1 RNA is ≥ 200 c/mL, the participant has met Protocol Defined Virologic Failure (PDVF) criteria (Section 7.1.1).[d] • If the repeat HIV-1 RNA is 50-199 c/mL, then discuss results with the ViiV medical monitor. If previous HIV-1 RNA result was ≥50 c/mL, the participant has met PDVF criteria (Section 7.1.1).

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 will be used for resistance testing. 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 in a time frame consistent with Section 7.1.1.1. 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 immediately.

4.1.2.2.2. Virtual Visits

Virtual visits may be conducted via phone, or via any video app (e.g., Skype, FaceTime, WhatsApp, Zoom), as allowed by local regulations.

Ideally, the participant will complete the CSSRS (via phone or computer) prior to the virtual contact by the site staff so that any alert for a positive response can be acted upon with the participant – to counsel or refer for additional assessment.

The discussion between site staff and the participant will include, at a minimum, those assessments outlined in the SoA (Section 1.3), as well as reminders regarding dose administration, the requirement for those on the GSK3640254 arms that the dose needs to be taken with a meal, study-preferred lifestyle restrictions (Section 5.3), instruction for the next virtual or in-clinic visit, as well as reminders for POCBP to perform an at-home, monthly pregnancy test and report the results to the site. Site staff should ask general questions to assess the emotional wellbeing of the participant, listening for cues for suicidal ideation and behavior (SIB) or any other unusual changes in behavior.

4.1.2.2.3. Primary Analyses and Optimal Dose Selection

The primary analysis will evaluate all available data as outlined in the endpoints for primary and secondary objectives. The Week 24 analysis of efficacy, safety/tolerability, PK and resistance will allow the Sponsor to determine an optimal dose for GSK3640254. The quantitative criteria used to evaluate success or futility based upon the Week 24 primary analysis (proportion of Virologic Responders, i.e., participants with HIV-1 RNA <50 c/mL) are described in Section 9.5.

After an optimal dose is selected by the Sponsor, a communication will be sent to Health Authorities/Ethics Committees for their information, where required or requested.

4.1.2.2.4. Potential cART Reimbursement after Last Dose of Study Treatment

Sponsor recognizes that the clinical goal is for all participants to achieve and maintain virologic suppression. When a participant is discontinued from the trial early, whether they are a Virologic Non-Responder at Week 24 or they are withdrawn early for any other reason, there may be situations where sites may be reimbursed for up to a 6-week supply of Investigator selected/prescribed antiretroviral medication to facilitate the transition of participants to non-study cART. Any brief duration of reimbursement longer than 6 weeks, expected to be in individual and rare circumstances, may be considered with Sponsor.

Specific direction will be provided by GSK Local Operating Company (LOC) personnel, who will determine for which country(ies) this is not a viable option, e.g., where reimbursement is not allowed by local regulations, or where acquisition of cART can be obtained without delay.

4.1.2.3. Switch to Optimal Dose

After the optimal dose has been chosen, and after the last participant completes their Week 48 visit, participants will move into the Non-Randomised Phase. Participants on

the GSK3640254 arms will change from the blinded dose to the open label optimal dose. Simultaneously, these participants will also be switched from the dual NRTI therapy to DTG. GSK3640254 participants will qualify to move into the open label, Non-Randomised phase if their most recent HIV-1 RNA <50 c/mL. Participants in the GSK3640254 Arms with their most recent HIV-1 RNA = 50-199 c/mL may be able to make this change as well, but only after site's consultation with the ViiV medical monitor, else they will be discontinued from the study.

Sponsor, with the Investigator, will assess clinical criteria (e.g., assessment of adherence by Investigator) and laboratory criteria (e.g., HIV-1 RNA and CD4+ T-cell count) relative to the risk/benefit ratio for continuation of each participant into the Non-Randomised Phase of the trial.

Thereafter, the trial will be fully open label with just 2 arms:

- Arms 1, 2 & 3 will switch to the Open Label GSK3640254 Optimal Dose + Open Label DTG

- Participants on the Open Label DTG + ABC/3TC or FTC/TAF arm will continue unchanged into the Non-Randomised Phase and their participation in the treatment phase will end as each individual participant reaches their Week 144 visit.

Participants on the blinded GSK3640254 arms will have their blinded GSK3640254 treatment switched to the optimal, open label dose of GSK3640254 at their next regular visit, or earlier if necessary (e.g., if one of the doses is identified as being suboptimal and it is determined that the switch should happen sooner). Investigators and participants will then be unblinded to participant's initial GSK3640254 dose as well as to the optimal dose of GSK3640254.

The trial at this point will be fully open label.

Data from this fully open, Non-Randomised Phase will provide long-term, comparative, descriptive information on durability of response, safety/tolerability, and resistance when GSK3640254 is given in combination with DTG.

4.1.3. Follow-up

When a participant withdraws/discontinues early (at any point prior to the end of the study, including Virologic Non-responders at Week 24), participants will be required to be seen in-clinic for a follow-up visit between 2 to 4 weeks after their last on-treatment visit. These data comprise an essential evaluation that needs to be done before discharging any participant from the study.

For participants who have reached the end of the study (DTG Reference arm = at Week 144; GSK3640254 Arm = when the study is declared to be at the end), the in clinic Follow-up visit will be conducted 2-4 weeks after the last dose of study medications for those who, at the last study visit, have ongoing AEs, SAEs regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to

the participant. Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality).

Beyond this follow-up visit (outside of the study), all AEs, SAEs and clinically relevant vitals, ECG findings, and lab abnormalities will be followed towards acceptable clinical resolution.

Participants who are withdrawn for reasons of safety should continue to be followed even beyond the study final, follow-up visit (outside of the study) to assess the outcome of the safety event that triggered discontinuation of study drug (as determined by the Investigator).

4.1.4. Study Completion

The study will be completed when either the development of GSK3640254 is discontinued or until GSK3640254 is locally approved and commercially available (anticipated to be in the year 2027).

Alternatively, this study could be completed at an earlier date and participants would continue in a rollover study that would be anticipated to be complete in 2027.

For study status purposes, a participant is considered to be complete if they attend the last on treatment visit at the end of study for participants in the GSK2640254 arm, and at Week 144 (for participants in the DTG reference arm). The Follow-Up visit is not required for successful completion of the study.

4.1.5. Optional Stomach Substudy (Esophagogastroduodenoscopy [EGD] with Biopsy and Serum Biomarkers)

To explore the monitoring of potential gastric toxicity in the stomach of HIV-1 infected participants, a substudy will explore the potential relationship (if any) between Serum Biomarkers and the occurrence of any findings on EGD on biopsy (see Exploratory Objective in Section 3).

The Day 1 EGD with Biopsy will likely need to be performed during the Screening Period since performing both this procedure and an entire Day 1 visit all on the same day is unlikely.

The Day 1 blood collection for Serum Biomarkers will be collected at the Day 1 visit.

An EGD with biopsy will be performed for Day 1 (baseline assessment [prior to first dose]; to be done in the Screening period once main study eligibility has been confirmed), and again for Week 24 and Week 96. It is reasonably expected that the procedure should be performed ± 2 weeks around the Week 24 and Week 96 visit milestones (and any other visit at which an EGD could additionally be requested [See Section 8.6.1]).

Specifically, this will be accomplished by participants voluntarily electing to take part in a Stomach substudy (e.g., signing a separate additional informed consent form [ICF]

agreeing to undergo the procedure at the GI facility). The Stomach substudy will seek to recruit approximately 7 participants from each of the 4 treatment arms, approximately 28 participants in total.

A gastroenterologist is expected to be a co-Investigator/sub-Investigator (where locally allowed and/or possible) with sites that will participate in this substudy. Not only will the participant sign a distinct Stomach Substudy Sponsor ICF, but also a consent as required by the facility of the gastroenterologist who will inform the participant of the risks, benefits, and alternatives of undergoing the procedure to ensure the participant is making an informed decision about their willingness to participate.

A certified endoscopist must determine that the participant is suitable to undergo the procedure. This will be accomplished by a separate, pre-procedural evaluation. This may include but is not limited to (as dictated by local SOC: history, physical examination (including airway examination), and noting allergies or prior adverse reaction to sedation. Additional unscheduled laboratory (e.g. pregnancy testing, coagulation studies, type/screen) and imaging (e.g. chest radiograph) assessments before or after the EGD are at the discretion of the endoscopist based upon patient risk factors [Pasha, 2014] and local SOC. The endoscopist must have appropriate facilities, equipment, and clinical staff support to ensure the safety of the participant pre-, peri-, and post-procedure. This includes but is not limited to: ongoing assessment of the participant's clinical condition and vitals, respiratory support, rescuing from over-sedation, and cardiopulmonary resuscitation).

The endoscopist will provide direction on NPO timing and administration of routine daily medications. The choice of pre-, peri-, and post-procedure medications will be left to the discretion of the endoscopist and be permitted at any point in the study. Drugs which prolong the QTc should be avoided. Participant monitoring may include vitals and level of sedation evaluation: pre-procedure, after sedatives/analgesics, at minimum of every 5 minutes during the procedure, during recovery, and before discharge (or as dictated by local SOC). Additional monitoring may include assessment of ventilator status and cardiac electrical activity [Early, 2018]. Post-procedure recovery instructions (e.g. limitations on driving or operating machinery) are at the discretion of the endoscopist [Levitzky, 2010].

Procedural details (including but not limited to gross findings, biopsies taken, and any intervention) of the EGD will be captured within an eCRF. Redacted endoscopic photographs, where allowed by local regulations, will be stored with the Sponsor. For additional details, please see the SRM.

Details of the optional Stomach Substudy biomarker needs are outlined in Section 8.6.1. Blood for this purpose will be collected at the regular clinic visits at Day 1 and at Weeks 24, 48 and 96.

The screening period may be extended for participants in the EGD substudy (see Section 5.5.1).

If a participant withdraws from the Stomach Substudy, they may still continue in the main study.

4.1.5.1. Stomach Substudy Enrollment Considerations

The Stomach Substudy, with EGD with biopsy and serum biomarkers, seeks to recruit 28 participants from the pool of 150 randomized.

Recruitment into the substudy will be monitored on an ongoing basis.

Given the nature of voluntarily electing to undergo an additional invasive procedure (in addition to all routine study evaluations and procedures), there is a probability that, even though the study has sufficiently screened enough participants to achieve 150 randomized, the Stomach substudy may not have recruited the goal of 28 participants total. In this event, the clinical study team may decide to leave the Screening period open (for approximately another 2 months, or until 30 additional participants have been screened, or until the substudy is filled, whichever comes first) to increase the clinical probability of recruiting more participants to voluntarily participate in the Stomach substudy. This, in an effort to arrive as close to the original target goal of 7 participants per treatment arm (28 in total).

This will be handled in the following manner:

- If the least number of participants within the substudy is 4-6 in any arm, Sponsor may decide to keep the enrollment period open as described above.

  OR

- If the least number of participants within the Stomach substudy is 1-3 in any arm, the study as a whole will not seek to enrol additional participants. This is because there is a lower clinical probability that a large proportion of the additional participants would volunteer to participate in the Stomach substudy.

Sponsor may also decide to let the Stomach Substudy over-enroll to account for any substudy discontinuations prior to the collection of the Week 24 sample (needed for the comparison to Day 1)

4.1.5.2. Stomach Substudy Criteria for Discontinuing an Individual Participant

A participant with the following findings on any EGD Biopsy sample (at any time) will be discontinued from the study if any of the following findings are encountered:

- Dysplasia
- Moderate inflammation and moderate intestinal metaplasia
- Severe changes seen in single cell necrosis of parietal cells, chief cell atrophy or cytoplasmic alteration, decreased cellularity of parietal cells or chief cells, inflammation, or Spasmolytic polypeptide-expressing metaplasia (SPEM).

4.1.5.3. Stomach Substudy Criteria for Stopping the Study

Overall trial stopping criteria (for stopping the substudy altogether) will be based upon all participants in the experimental arms participating in the Stomach Substudy (regardless of any other criteria, e.g. efficacy):

- ≥ 1 participant with any degree of Dysplasia in any treatment arm
- ≥ 4 participants with moderate inflammation and moderate Intestinal Metaplasia
- ≥ 4 participants with severe changes seen in single cell necrosis of parietal cells, chief cell atrophy or cytoplasmic alteration, decreased cellularity of parietal cells or chief cells, inflammation, or SPEM.

4.2. Scientific Rationale for Study Design

208379 is a Phase 2b, dose-range finding assessment of 100 mg, 150 mg and 200 mg once-daily doses of GSK3640254 administered with food. Based on available GSK3640254 data, including in vitro virology, PK, antiviral activity/resistance, and safety/tolerability data from completed clinical trials, doses 100 mg, 150 mg and 200 mg are anticipated to provide adequate antiviral activity/efficacy and be well-tolerated (in combination with ABC/3TC or FTC/TAF). The primary endpoint will assess efficacy by determining the proportion of virologic responders (participants with plasma HIV-1 RNA <50 c/mL at Week 24). HIV-1 RNA is highly predictive of meaningful clinical benefit [U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2015].

The approved ARVs (ABC/3TC, FTC/TAF) and the DTG-based control arm chosen for this study are accepted agents for initiation of antiretroviral therapy in treatment guidelines [European AIDS Clinical Society Guidelines, 2020; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019] and, as such, are considered appropriate for this trial.

4.2.1. Community Experts Input into Design

Input from community experts revealed their understanding of the clinical and scientific justifications for the visit schedule, and for the assessments and procedures that participants will undergo.

Input also revealed the desire to maintain realistic expectations of the patient population in a long-term study. Based on that feedback, this study does not include restrictive requirements for alcohol, tobacco and marijuana, rather, suggestions for study-preferred limits that should be highly encouraged at each visit.

4.3. Justification for Dose

The planned doses for this Phase 2b study (100 mg, 150 mg, and 200 mg QD administered with food) were selected based on population PK and exposure-response (E-R) modelling and clinical trial simulations of antiviral effect as described in this section. The doses were targeted to achieve a minimum of 75% of maximum effect

predicted at day 8 and to maintain steady-state Cτ above the 3-times protein binding-adjusted EC90 (3xPBAEC90) target of 0.11 µg/mL (in-vitro EC90 value for *in-vitro* virus containing R361K/V362I/L363M substitutions) in 95% of the subjects.

A population pharmacokinetic model was developed using the single dose (1 – 400 mg) and multiple dose (50-320 mg QD for 14 days) data from healthy subjects from the FTIH study 207187, as well as the multiple dose data in HIV-1 infected subjects (10 mg – 200 mg QD for 7-10 days). All doses were administered with a moderate-fat meal. The pharmacokinetics of GSK3640254 (given with food) was described by a two-compartment model with sequential zero-order absorption (in the depot compartment) followed by first order absorption (from depot to the central compartment) and first order elimination. Inter-individual variability was estimated on the apparent oral clearance (CL/F), apparent volume of distribution of the central compartment (V2/F), intercompartmental clearance (Q/F), absorption rate constant (Ka), and duration of the zero-order process (D1). The CL/F and V2/F were scaled using fixed allometric coefficients of 0.75 and 1, respectively. Weight was found to be a significant covariate on Ka. In addition, Study (as a surrogate for subject type and GSK3640254 salt differences) was also found to be significant covariates on bioavailability (F was ~27% lower in the FTIH study compared to that from the PoC). Evaluation of the post-hoc individual estimates of Cmax, AUC and Cτ indicated that model-estimated PK parameters were comparable to the observed values.

The objective of the E-R analysis was to characterize the relationship between antiviral activity and exposure of GSK3640254 in HIV-1 infected subjects, and to determine the effect of key covariates (including baseline EC50, baseline viral load, baseline CD4 and CD8 T-cell counts) on GSK3640254 antiviral activity. The E-R analysis was conducted using the data from the Phase 2a study 208132 (up to day 8/9 [Visit 5] in Part 1 and up to day 8 [Visit 6] in Part 2. All doses were administered with a moderate-fat meal. The decline in HIV-1 RNA over 7 or 10 days (and the treatment emergent genotypic and phenotypic changes) in HIV-1 infected treatment naïve adults is described in Section 2.2.4.

The E-R was assessed via an inhibitory Emax model using the observed average steady-state Cτ and maximum viral load decline from baseline. None of the screened covariates were found to be significant and therefore were not included in the full covariate model.

The population PK model of GSK3640254 was integrated with the E-R model and short-term clinical trials simulations were conducted (500 trials with 60 subjects/ dose level mrgsolve_0.8.9 package in R version 3.2.5) by sampling from the multivariate normal distribution and covariance matrix to include both uncertainty in parameter estimates and inter-subject variability. It was assumed that the bioavailability of GSK3640254 in Ph2b will be similar to that from study 208132. For each individual, the anticipated response (maximum viral load decline) and percent of maximum effect was estimated. Simulations were then summarized by computing the median percent of maximum effect for each dose across the trials. The results of the simulations summarized in Table 5 indicate that doses ≥100 mg QD administered with food are predicted to result in a median percent of maximum effect at day 8 of at least 75%. In addition, a 300 mg QD dose is not predicted

to provide a significant increase in predicted % of maximum effect compared to the 200 mg dose.

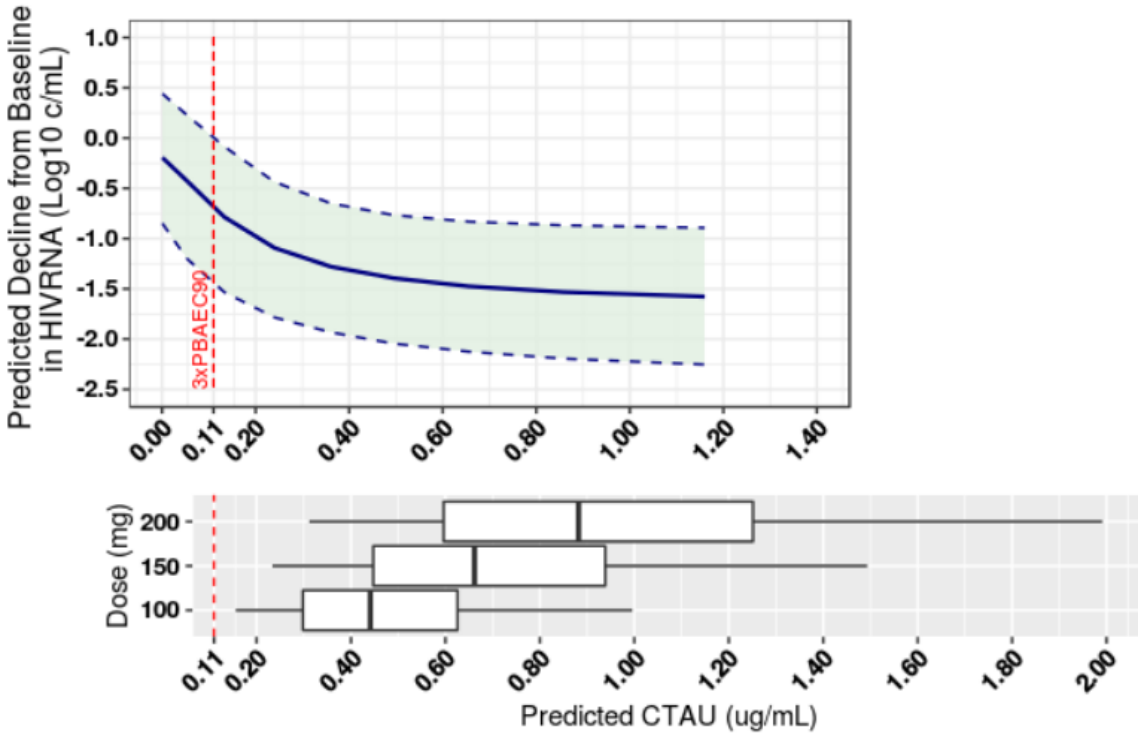
Table 5 Predicted Median Percent of Maximum Effect [90% PI] at Day 8 for GSK3640254 Doses Ranging from 75 mg to 300 mg QD administered with food (500 trials with n=60 subjects per dose level)

Dose (mg)	Median [5%, 95%] Percent of Maximum Effect
75	70.4 [47.5, 95.4]
100	78.0 [54.5, 98.1]
125	83.1 [61.4, 99.6]
150	86.4 [66.6, 101]
200	90.4 [73.1, 102]
300	94.2 [80.1, 103]

PI = Prediction Interval

Figure 2 depicts the predicted decline in viral load versus Cτ at Day 8 and boxplot summary of predicted Cτ by proposed dose levels.

Figure 2 Simulated Predicted Decline in HIV-1 RNA versus Predicted Cτ at Day 8



Top panel – Dashed and solid blue lines are 5th, 95th and median of simulated data, respectively. Shaded area is the 90% prediction interval of simulated data. Bottom panel – the middle bar inside the boxes represents the median; the ends of the boxes are the 25th and 75th percentiles; the whiskers are the 5th and 95th percentiles of simulated Cτ. The red dashed line in both panels represents the 3xPBAEC90 (determined in-vitro based on virus with R361K/V362I/L363M substitutions).

Table 6 presents the model-predicted steady-state GSK3640254 PK parameters at the planned doses following QD administration with food. As expected, the predicted PK parameter values for the maximum proposed dose of 200 mg QD administered with food fall within the observed 95% CI of the geometric mean PK parameters from the PoC study 208132 (Table 3 in Section 2.2.4). The associated inhibitory quotient (IQ) for each dose was calculated by dividing Cτ median [5th – 95th percentiles] by the 3xPBAEC90 (Table 6).

The results show that all proposed doses are predicted to result in Cτ values >3xPBAEC90 in more than 95% of the subjects (i.e. Cτ 5th percentile for the 100 mg dose >0.11 μg/mL) (Table 6). In addition, the planned doses provide a median IQ ranging from 4 – 8. Taking into account the variability in parameter estimates, the predicted IQ over the proposed doses ranges from 1.4 to 18.2. By comparison, for GSK3532795, a previous generation MI, the median IQ in phase 2b (calculated as Cτ/1xPBAEC90 based on in-vitro Δ370 virus) for the 180 mg QD dose (maximum tested dose) was approximately 1.5. Therefore, assuming a biologically plausible correlate between Day 8 antiviral response and Week 24 efficacy, when GSK3640254 is combined with two potent NRTIs (ABC/3TC or FTC/TAF), the response rate at week 24 is likely to be similar or better than GSK3532795 180 mg QD (i.e. >82.4% for week 24 snapshot <40c/mL).

Table 6 Predicted Steady-State PK Parameters Median [90% PI] Following Once a Day Dosing of GSK3640254 with Food and Associated IQ

Dose (mg)	Median [5th – 95th Percentiles] [1]			
	Cmax (μg/mL)	AUC(0-24) (μg.h/mL)	Cτ (μg/mL)	IQ (Fold Above 3xPBAEC90)[2]
100	1.11 [0.652-1.9]	15 [8.2-27]	0.442 [0.153-0.999]	4 [1.4 - 9.1]
150	1.67 [0.978-2.85]	23 [12-41]	0.663 [0.23-1.5]	6 [2.1 - 13.6]
200	2.22 [1.3-3.8]	30 [16-54]	0.883 [0.307-2]	8 [2.8 - 18.2]

PI = Prediction Interval
[1]All simulations included uncertainty and inter-subject variability in parameter estimates.
[2] 3xPBAEC90 = 0.11 μg/mL based on in-vitro virus containing R361K/V362I/L363M substitutions.

Calculated Fold Coverage for Selected Doses

Predicted GSK3640254 safety coverage based on NOAEL and LOAEL exposure in the non-clinical chronic toxicity studies in rat and dog for the at the planned doses given once daily with food are presented in Table 7.

Table 7 Predicted Safety Cover Following Once a Day Dosing of GSK3640254 with Food

Dose (mg)	Fold cover dog NOAEL:human AUC(0-24) [1]	Fold cover rat LOAEL:human AUC(0-24) [2]	Fold cover dog LOAEL:human AUC(0-24)[3]
100	0.56	1.26	3.1
150	0.36	0.82	2.0
200	0.28	0.63	1.6

[1] Based on dog NOAELmean AUC of 8.37 from non-clinical chronic studies and the model-predicted median AUC (Table 6).
[2] Based on rat LOAEL mean AUC of 18.9 µg.h/mL from non-clinical chronic studies and the model-predicted median AUC (Table 6).
[3] Based on dog LOAEL mean AUC of 46.4 µg.h/mL from non-clinical chronic studies and the model-predicted median AUC (Table 6).

At the highest planned dose of 200 mg QD, the model-based predicted exposure corresponds to 0.3-fold the NOAEL (AUC = 8.37 ug.hr/mL) in dogs, 0.63-fold the LOAEL in rats (AUC = 18.9 ug.hr/mL) and 1.6-fold the LOAEL in dogs (AUC = 46.6 ug.hr/mL) from chronic toxicity studies (See Section 2.2.2) (Table 7). All microscopic findings in the stomach of rats and dogs and changes in serum gastrin were shown to be partially reversible following a 4-week recovery period. Potential effects in the stomach of humans during clinical trials are being investigated in a gastric safety substudy (See Section 1.3 and Section 8.6.1) with appropriate clinical monitoring (See Section 2.2, Section 4.1.5, and Section 8.6).

With regard to potential for QT prolongation, as noted in Section 2.3, in the concentration-QTc analysis using the Multiple Ascending Dose data collected in the FTIH study 207187, a QTcF effect above 10 ms could be excluded up to GSK3640254 mean plasma concentrations of approximately 2000 ng/mL, which corresponds to doses of approximately 200 mg (Table 3 and Table 6). The cardiovascular risk mitigation strategy for QT prolongation is described in Section 2.3.1.

Evaluated and anticipated Drug Interactions Between GSK3640254 and coadministered ARVs

In this Phase IIb study, investigators will choose either FTC/TAF or ABC/3TC fixed dose combination as the allowed NRTI backbone for use in combination with GSK3640254.

DDI risk with FTC/TAF

As emtricitabine and tenofovir are primarily eliminated by renal mechanisms with the majority of drug eliminated unchanged in the urine, a drug interaction with GSK3640254 is not anticipated with these NRTIs. However, as unexpected drug interactions have been reported between tenofovir and other antiviral therapy agents, a one-way drug interaction clinical study was conducted to evaluate the potential impact of GSK3640254 on FTC/TAF (208134) [GlaxoSmithKline Document Number 2018383314_00]. Results from this study showed that GSK3640254 does not affect the steady-state plasma concentrations of TAF, tenofovir (TFV) or FTC. In addition, the PK of GSK3640254 in this study were similar to what has been observed previously .

DDI risk with ABC/3TC

ABC and 3TC are not significantly metabolised by CYP enzymes nor do they inhibit or induce this enzyme system. The primary pathways of ABC metabolism in human are by alcohol dehydrogenase (~30%) and by glucuronidation (~36%). These metabolites are excreted in the urine. Lamivudine is predominantly eliminated by active organic cationic secretion. Therefore, the likelihood of metabolic interactions between GSK3640254 with ABC or 3TC is low.

3TC and ABC demonstrate no or weak inhibition of the OATP1B1, OATP1B3, BCRP and Pgp or and toxin extrusion protein 2-K (MATE2-K). In addition, 3TC demonstrates no or weak inhibition of the drug transporters MATE1or OCT3 and ABC demonstrates minimal inhibition of organic cation transporter 1 (OCT1) and organic cation transporter 2 (OCT2). 3TC and ABC are therefore not expected to affect the plasma concentrations of GSK3640254 in the event that it is a substrate of these transporters. In addition, although ABC is an inhibitor of MATE1 and 3TC is an inhibitor of OCT1 and OCT2 in vitro, they have low potential to affect the plasma concentrations of substrates of these transporters at therapeutic drug exposures (up to 600 mg for abacavir or 300 mg for lamivudine).

In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, MRP2 or MRP4 therefore potential modulation of these transporters by GSK3640254 is not expected to affect ABC plasma concentrations.

Although ABC and 3TC are substrates of BCRP and Pgp in vitro, clinical studies demonstrate no clinically significant changes in ABC pharmacokinetics when coadministered with lopinavir/ritonovir (Pgp and BCRP inhibitors) and inhibitors of these efflux transporters are unlikely to affect the disposition of 3TC due to its high bioavailability. 3TC is an in vitro substrate of MATE1, MATE2-K and OCT2. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase 3TC 3TC plasma concentrations however; the resulting increase was not clinically significant. 3TC is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of 3TC, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

DDI risk with DTG

A Phase 1, two-way drug interaction study with GSK3640254 and DTG showed no effect on plasma GSK3640254 PK. GSK3640254 200 mg QD increased plasma DTG AUC(0-τ), Cmax and Cτ by 17%, 9%, and 24%, respectively. These increases were not considered clinically meaningful.

In summary, based on the lack of observed or predicted clinically meaningful drug interactions, GSK3640254 can be administered with either NRTI backbone or DTG combinations without dose adjustments.

Assessment of the Change in Formulation and Effect of Food

The recently completed Phase 2a clinical trial (208132) utilized capsules; this Phase 2b will use tablets. Study 213567 was a relative bioavailability and food effect study performed to compare the exposures between the GSK3640254 tablet and capsule in the presence of moderate fat meal and to investigate the effect of food on the PK of the GSK3640254 tablet. As shown in Table 8, the tablet provided similar exposures to the capsule when both were given with food.

Table 8 Assessment of Relative Bioavailability: Preliminary Statistical Comparison of Plasma GSK3640254 PK Parameters Based on Nominal Time (Study 213567)

PK Parameter	Ratio of GLS Means for Test vs. Reference [90%CI] (%Ref)
AUC(0-∞) h*μg/mL	99.8 [92.6, 108]
AUC(0-t) h*μg/mL	100 [93.2, 108]
Cmaxμg/mL	109 [98.8, 121]

1. Ref: Treatment A; Test: Treatment B

Treatment A: GSK3640254 200 mg (capsules) administered under moderate fat conditions.
Treatment B: GSK3640254 200 mg (tablets) administered under moderate fat conditions.

The summary of the statistical analysis for the assessment of food effect presented in Table 9 shows that GSK3640254 AUC(0-∞) and Cmax values following administration of the tablet with a moderate fat meal are 345% to 484% higher relative to administration in a fasted state, respectively. In addition, GSK3640254 AUC(0-∞) and Cmax following administration of the tablet with a high fat meal is 306% to 365% higher relative to administration in fasted state, respectively.

Table 9 Assessment of Food Effect: Preliminary Statistical Comparison of Plasma GSK3640254 PK Parameters Based on Nominal Time (Study 213567)

PK Parameter	Test vs Ref	Ratio of GLS Means for Test vs. Reference [90%CI] (%Ref)
AUC(0-∞) h*μg/mL	C vs D	345 [288, 413]
	E vs D	306 [256, 366]
AUC(0-t) h*μg/mL	C vs D	378 [318, 449]
	E vs D	335 [282, 399]
Cmaxμg/mL	C vs D	484 [391, 599]
	E vs D	365 [295, 451]

Treatment C: GSK3640254 200 mg (tablets) administered under moderate fat conditions (test).
Treatment D: GSK3640254 200 mg (tablets) administered under fasted conditions (ref).
Treatment E: GSK3640254 200 mg (tablets) administered under high fat conditions (test).

In summary, the results from the RBA and food effect study indicate that no dose adjustments are required due to the change in formulation based on:

- The similarity in PK parameters between the tablet used in this Phase 2b study and the capsule used in the Phase 2a in the presence of a moderate fat meal.
- The dose predictions are based on modelling of the data from studies in which GSK3540254 was administered with food.

In conclusion, the GSK3640254 dose range is anticipated to study a range of exposures which should provide therapeutic benefit (virologic suppression and antiviral activity) while being well tolerated (in combination with ABC/3TC or FTC/TAF and subsequently DTG).

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the VH Investigational Product (IP) or other study treatment that may impact participant eligibility is provided in the current IB [GlaxoSmithKline Document Number 2018N379610_02] for GSK3640254, and in the current prescribing information for Epzicom (ABC/3TC) [Epzicom USPI, 2019], Descovy (FTC/TAF) [Descovy USPI, 2019 and Tivicay [Tivicay USPI, 2020].

The generation of geno/phenotype results from Monogram Biosciences (see Section 8.6.2) can be affected by several factors (including but not limited to shipping delays and repeating of steps within the PCR process), resulting in reporting delays that can jeopardize the ability of a participant to be randomized within their Screening window. To mitigate this issue, the following actions may be taken:

a. The 42-day Screening period may be extended to a maximum of 63 days while awaiting the Monogram results. See Section 5.5.
b. There may be cases where local resistance test results may be used to determine eligibility. VH (Clinical Virologist) will review any local test results and the methodology used to determine if the results are suitable for use in this trial. The (sole) decision of VH will be final. See details in the SRM.
c. Note: the Monogram Biosciences PSGT result will still be reported in usual fashion. In the unlikely event of a discordant result (local test genotypically susceptible and PSGT net assessment resistant), the randomized participant will be withdrawn from the study.

Rescreen: Participants are allowed to rescreen for this study one time with the exception of clinically irreversible findings in Screening; examples include but are not limited to: presence of *HLA-B*5701* allele, liver cirrhosis, CDC Stage 3 disease, drug allergy/sensitivity, significant psychiatric disorder, cardiac arrythmias, or established archived drug resistance. See Section 5.4.

When a participant has to be rescreened, the Monogram results from the prior 208379 Screening period may be used to determine eligibility (though the Monogram samples for the Rescreen should still be collected, results of which, too, should eventually be filed).

Retest: A single repeat test (retest) per laboratory analyte is allowed during a single Screening period to determine eligibility (with the exception of Screening genotype/phenotype, HLA testing or other, as determined by the medical monitor).

Pre-procedure evaluations/assessments done/requested by the gastroenterologist prior to each of the EGDs should be done only once.

5.1. Inclusion Criteria

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

Age

1. Participants must be 18 years of age inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

2. Treatment-naïve, defined as no ARVs (in combination or monotherapy) received after the diagnosis of HIV-1 infection (e.g., use of PreP meets inclusion);
3. Documented HIV infection and Screening plasma HIV-1 RNA ≥1000 copies/mL;
4. Screening CD4+ T-cell count ≥250 cells/mm^3;
5. Antiviral susceptibility to the NRTI backbone selected should be demonstrated

Weight

6. Body weight ≥50.0 kg (110 lbs.) for men and ≥45.0 kg (99 lbs) for women and body mass index (BMI) > 18.5 kg/m^2. Calculations will utilize sex assigned at birth.

Sex

7. Participants who are male at birth and participants who are female at birth

   *NOTE: There are no contraceptive requirements for participants who are male at birth.

   a. Participants who are female at birth

      Contraceptive use by participants who are female at birth should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

      - A participant who is female at birth is eligible to participate if they are not pregnant or breastfeeding, and one of the following conditions applies:
        - Is a participant of non-childbearing potential (PONCBP) as defined in Section 10.4, Contraceptive and Barrier Guidance;
          OR

- Is a POCBP (as defined in Section 10.4) and using an acceptable contraceptive method as described in Section 10.4.2 during the study intervention period (at a minimum until after the last dose of study intervention). The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention.
  - If a hormonal method is selected, the participant is required to be clinically stable on it for at least one month prior to starting treatment in the study.

- A POCBP must have a negative highly sensitive serum pregnancy test 42 days before the first dose of study intervention. See Section 8.2.5 Pregnancy Testing.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5.
- 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

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other

9. **For participants enrolled in France**: a participant will be eligible for inclusion in this study only if either 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:

Medical Conditions

1. 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;
2. 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;

   Note: Other localized malignancies require agreement between the investigator and the ViiV Medical Monitor for inclusion.
3. Presence of primary HIV-1 infection, evidenced by acute retroviral syndrome (e.g., fever, malaise, fatigue, etc.) and/or evidence of recent (within 3 months) documented viremia without antibody production and/or evidence of recent (within 3 months) documented seroconversion;

4. Known history of liver cirrhosis with or without viral hepatitis co-infection;
5. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)
6. History of ongoing or clinically relevant hepatitis within the previous 6 months;
7. History of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation;
8. Any history of significant underlying psychiatric disorder, in the opinion of the Investigator or ViiV Medical Monitor, including but not limited to schizophrenia, bipolar disorder with or without psychotic symptoms, other psychotic disorders, or schizotypal (personality) disorder; or a clinical assessment of suicidality based on the responses on the eCSSRS;
9. Any history of major depressive disorder with or without suicidal features, or anxiety disorders, that required medical intervention (pharmacologic or not) such as hospitalization or other inpatient treatment and/or chronic (>6 months) outpatient treatment;

    Note: Participants with other conditions such as adjustment disorder or dysthymia that have required shorter term medical therapy (<6 months) without inpatient treatment and are currently well-controlled clinically or resolved may be considered for entry after discussion and agreement with the ViiV Medical Monitor.
10. Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the Investigator or ViiV Medical Monitor (with or without psychiatric evaluation), could interfere with the participant’s ability to comply with the dosing schedule and protocol evaluations or which might compromise the safety of the participant;
11. A pre-existing condition, in the opinion of the Investigator or ViiV Medical Monitor, that could interfere with normal gastrointestinal anatomy or motility (e.g., gastroesophageal reflux disease [GERD], gastric ulcers, gastritis, inflammatory bowel disease), hepatic and/or renal function, or with the absorption, metabolism, and/or excretion of the study drugs or render the participant unable to take oral study treatment;
12. Myocardial infarction in the past 3 months;
13. Familial or personal history of long QT syndrome or sudden cardiac death;
14. Medical history, current or historical, of significant cardiac arrhythmias or ECG findings which, in the opinion of the Investigator or ViiV Medical Monitor, will interfere with the safety of the participant;

    Note: Examples of ECG findings include symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained ventricular tachycardia (VT) or sustained VT, second degree atrioventricular block (AVB) Mobitz Type II, or third degree AVB.

Prior/Concomitant Therapy

15. Active Treatment for a viral infection other than HIV-1, such as Hepatitis B, with an agent that is active against HIV-1 (were known to be infected with HIV-1 after treatment for Hepatitis B was completed);
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. Participants receiving any protocol-prohibited medication and who are unwilling or unable to switch to an alternate medication;
19. Participants who are unwilling to stop any medications as required by the local lab test for *H. pylori.*
20. Participants who require concomitant medications known to be associated with a prolonged QTc (see list from https://www.crediblemeds.org).

Prior/Concurrent Clinical Study Experience

21. Exposure to an experimental drug, human blood product, monoclonal antibody, or vaccine (which does not have emergency, conditional, or standard market authorization) within 28 days prior to the first dose of study treatment;

    Note: Consult with the Medical Monitor if clarification is needed. Treatment with a SARS-CoV-2 vaccine that has received emergency, conditional, or standard market authorization is allowed if the principal investigator (PI) determines that the benefit-risk profile for that individual study participant is favourable. The use of other investigational COVID vaccines that have not received emergency, conditional, or standard market authorization and are still only used in clinical trials will not be allowed at this time.
22. Current enrollment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study intervention (including an investigational COVID vaccine) or any other type of medical research.

Diagnostic assessments

23. Any evidence of viral resistance based on the NRTI backbone selected
24. Historical evidence (prior to study screening period) of the presence of resistance-associated mutations gag A364V or A364A/V
25. Creatinine Clearance <50 mL/min;
26. ALT ≥ 3x ULN or ALT ≥ 2x ULN and total bilirubin ≥ 1.5x ULN (upper limit of normal)
27. Evidence of Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs) and reflex HBV DNA as follows:

a. Participants positive for HBsAg are excluded;
b. Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA on reflex testing 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.

See SRM for additional details.

28. Positive Hepatitis C antibody test result at Screening AND positive on reflex to Hepatitis C RNA;

    Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained

29. Positive test results for *Helicobacter pylori* [Chey, 2017];

    Note: Participants who test positive for *H. pylori* can be treated/eradicated and retested with the same Screening period. The repeat test for *H. pylori* must be done no sooner than 28 days after the last dose of antibiotic treatment for the infection [Chey, 2017].

30. Known or suspected active COVID-19 infection OR contact with an individual with known COVID-19, within 14 days of study enrollment (WHO definitions Section 10.11.5.2.1). Note, this study does not require a negative molecular test for SARS-CoV-2 for entry into the study.

31. Untreated syphilis infection [positive rapid plasma reagin (RPR) at Screening] without documentation of treatment.

    Note: Patients with a known syphilis infection can be Screened for the study no sooner than 14 days after the last dose of treatment for the syphilis infection. Participants who are assessed to have syphilis by the Screening tests can be treated within the Screening period, though the start of study treatment can be no sooner than 30 days after the last dose of treatment for the syphilis infection.

32. Presence of moderate-to-severe hepatic impairment (Class B or C) as determined by Child-Pugh classification (see Section 10.7);

33. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator or ViiV Medical Monitor, would preclude participation in the study of an investigational compound;

34. Urine Drug Screen positive (showing presence of): Amphetamines, Barbiturates, Cocaine, MDMA, or Phencyclidine, or non-prescribed opiates, oxycodone, benzodiazepines, methadone, methamphetamines, or tricyclic antidepressants;

    Notes:

    If the urine drug screen shows the presence of opiates, oxycodone, benzodiazepines, methadone, methamphetamines, or tricyclic antidepressants that are prescribed, the participant can be considered for the trial at the discretion of the Investigator recognizing at the time of enrollment: no studies on relevant drug interaction or GSK3640254 absorption-distribution-metabolism-elimination (ADME) will have been completed.

A positive result for THC is not exclusionary, though the PI should assess usage and only refer for the treatment phase those participants who seem appropriate for the trial, i.e., whose use of marijuana would not interfere with the participant's ability to comply with the required daily dosing schedule and protocol evaluations, or that might compromise the safety of the participant.

35. Any clinically relevant Grade 4 laboratory abnormality at Screen, including results for creatine phosphokinase (CPK), and lipid abnormalities that lack a compelling explanation from the Investigator;

    Note: Grade 4 CPK and lipid abnormalities that are explained by the Investigator, and with assent from the ViiV Medical Monitor, will not exclude the participant.

36. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 28 days;
37. Exposure to more than 4 new investigational drugs or vaccines (exclusive of a SARS-CoV-2 potential indication) within 12 months prior to the first dosing day;
38. Treatment with radiation therapy or cytotoxic chemotherapeutic agents or any systemic immunosuppressive agent within 30 days of study drug administration or anticipated need for such treatment within the study;
39. ECG Heart Rate <50 bpm or >100 bpm, or QTcF >450 msec;

    Notes:
    - A heart rate of <50 or >110 is exclusionary and cannot be rechecked to determine eligibility.
    - A heart rate from 101 - 110 bpm can be rechecked by a single repeat ECG or by vitals within 30 minutes to verify eligibility.
    - The QT interval is corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually over-read by the Investigator. QTcF is used to determine eligibility and discontinuation for a participant in this study.
    - The Investigator's or ViiV Medical Monitor's over-read can supersede that of the machine at any time.

40. FOR PORTUGAL ONLY: HIV-2 infection (either determined by prior testing, medical history, or obtained locally during the Screening window)

Other Exclusions

To assess any potential impact on participant eligibility with regard to safety, the Investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study interventions.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Dose administration with GSK3640254 is required to be taken with a low-fat meal (may include but not limited to 400-500 calories, with 25% calories from fat) [FDA, 2019].

5.3.2. Alcohol, Tobacco and Marijuana

- It is suggested that alcohol consumption should be limited throughout study participation to the following: An average weekly intake of <14 drinks for participants assigned as male at birth or <7 drinks for participants assigned as female at birth. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
- Only clinically minor to moderate use (as determined by the PI/SI) of tobacco products will be allowed during study participation.
- Participants should refrain from the use of marijuana.

5.3.3. Activity

Participants will abstain from strenuous exercise for 24 hours before each clinic visit to reduce the chances of seeing a high CPK result in the study lab results.

See Section 10.9.5 for follow up assessments for elevated CPK.

5.3.4. Counsel regarding safe sex practices

All participants should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods and on the risk of HIV transmission to an uninfected partner.

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, any/all eligibility criteria that have not been met, and any serious SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened an additional time if, in the opinion of the Investigator, a current clinical outlook of the participant seems favorable for study inclusion (and if the participant never received study medication in this trial). Rescreened participants will be assigned a new participant number and will sign a new ICF(s).

As noted in Section 5, clinically irreversible findings found during screening would result in the individual not being screened a second time; examples include but are not limited to: liver cirrhosis, CDC Stage 3 disease, drug allergy or sensitivity, significant psychiatric disorder, cardiac arrythmias, or established, archived drug resistance.

5.5. Criteria for Temporarily Delaying Randomization

The Screening period may be extended up to a maximum of 63 days for those participating in the optional Stomach Substudy for the purpose of accommodating any

scheduling issues for the procedure, or if more time is needed to obtain results needed to determine eligibility.

5.5.1. Delaying Randomization for EGD Scheduling

It is anticipated that the EGD procedure will not be able to be performed on the same day as the Day 1 clinic visit for the main study. It will need to be performed during the Screening period. The intent is to get a baseline assessment, regardless of the visit designation.

The participant's overall eligibility for the main study should be confirmed prior to the participant undergoing the EGD procedure during the Screening period. Ideally, the procedure should be scheduled as soon as possible for a date occurring during the 42-day Screening period after all lab results are expected to be available so that main study eligibility can be confirmed prior to proceeding with the EGD procedure.

However, if the EGD cannot be scheduled within that 42-day timeframe, the EGD can be scheduled within an extended period of time, as long as the Day 1 start date for the main study can be accomplished on or before the maximum extension period of 63 days.

5.5.2. Delaying Randomization – Other

The Screening period may be extended beyond 42 days to a maximum of 63 days to account for additional time needed to determine eligibility. Examples include but are not limited to (subject to approval from the Medical Monitor): awaiting delayed Monogram results, allowing time for treatment for *H. pylori* and the subsequent retest, allowing time for the treatment of syphilis.

5.5.3. Contemporary lab results

If a Screening Period will be extended into the Day 43 – Day 63 timeframe, most Screening labs will need to be repeated to have a more current clinical picture of the participant.

- Chemistry, hematology (preferably), HIV RNA, lymphocyte subsets should be repeated so that the results can be available to reassess eligibility by those results. New results override those done previously in the Screening period. At the time of Day 1, these results cannot be more than 42 days old.

- HBV, HCV, HLA-B*5701 allele testing, geno/phenotype testing, lipids, RPR, PT/INR should not be repeated.

- A repeat of the Urine Drug Screen is at the discretion of the Investigator. New results override those done previously in the Screening period.

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.

6.1. Study Intervention(s) Administered

Randomised Phase

Arm 1	GSK3640254 100 mg + ABC/3TC or FTC/TAF	GSK3640254 100 mg + ABC/3TC or FTC/TAF	GSK3640254 100 mg + ABC/3TC or FTC/TAF	
Intervention Name	GSK3640254	Placebo to match GSK3640254	ABC/3TC (The clinical label will state Abacavir/ Lamivudine, 600mg/300mg to match the SPC)	FTC/TAF (The clinical label will state emtricitabine/ tenofovir alafenamide 200 mg / 25 mg to match the SPC)
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strength(s)	100 mg	0mg	abacavir 600 mg / lamivudine 300 mg	emtricitabine 200 mg / tenofovir alafenamide 25 mg
Dosage Level(s)	One tablet per day	Two tablets per day	One tablet per day	One tablet per day
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Background	Background

IMP and NIMP	IMP	IMP	IMP where provided centrally; Otherwise dependent on local regulations.	IMP where provided centrally; Otherwise dependent on local regulations.
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor or Locally sourced.	Provided centrally by Sponsor or Locally sourced.
Packaging and Labeling	32 tablets per HDPE bottle, labelled per country requirement	32 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement
Arm 2	**GSK3640254 150 mg + ABC/3TC or FTC/TAF**	**GSK3640254 150 mg + ABC/3TC or FTC/TAF**	**GSK3640254 150 mg + ABC/3TC or FTC/TAF**	
Intervention Name	GSK3640254	GSK3640254	ABC/3TC (The clinical label will state Abacavir/ Lamivudine, 600mg/300mg to match the SPC)	FTC/TAF (The clinical label will state emtricitabine/ tenofovir alafenamide 200 mg / 25 mg to match the SPC)
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strength(s)	100 mg	25 mg	abacavir 600 mg / lamivudine 300 mg	emtricitabine 200 mg / tenofovir alafenamide 25 mg
Dosage Level(s)	One tablet per day	Two tablets per day	One tablet per day	One tablet per day
Route of Administration	Oral	Oral	Oral	Oral

Use	Experimental	Experimental	Background	Background
IMP and NIMP	IMP	IMP	IMP where provided centrally; Otherwise dependent on local regulations.	IMP where provided centrally; Otherwise dependent on local regulations.
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor or Locally sourced.	Provided centrally by Sponsor or Locally sourced.
Packaging and Labeling	32 tablets per HDPE bottle, labelled per country requirement	32 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement
Arm 3	**GSK3640254 200 mg + ABC/3TC or FTC/TAF**	**GSK3640254 200 mg + ABC/3TC or FTC/TAF**	**GSK3640254 200 mg + ABC/3TC or FTC/TAF**	
Intervention Name	GSK3640254	Placebo to match GSK3640254	ABC/3TC (The clinical label will state Abacavir/ Lamivudine, 600mg/300mg to match the SPC)	FTC/TAF (The clinical label will state emtricitabine/ tenofovir alafenamide 200 mg / 25 mg to match the SPC)
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strength(s)	100 mg	0mg	abacavir 600 mg / lamivudine 300 mg	emtricitabine 200 mg / tenofovir alafenamide 25 mg
Dosage Level(s)	2 tablets per day	1 tablet per day	One tablet per day	One tablet per day

Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Background	Background
IMP and NIMP	IMP	IMP	IMP where provided centrally; Otherwise dependent on local regulations.	IMP where provided centrally; Otherwise dependent on local regulations.
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor or Locally sourced	Provided centrally by Sponsor or Locally sourced.
Packaging and Labeling	32 tablets per HDPE bottle, labelled per country requirement	32 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement

Arm 4 / Reference Arm	**DTG + ABC/3TC or FTC/TAF**	**DTG + ABC/3TC or FTC/TAF**	
Intervention Name	Tivicay (The clinical label will state Dolutegravir 50mg to match the SPC)	ABC/3TC (The clinical label will state Abacavir/ Lamivudine, 600mg/300mg to match the SPC)	FTC/TAF (The clinical label will state emtricitabine/ tenofovir alafenamide 200 mg / 25 mg to match the SPC)
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	Dolutegravir 50 mg	abacavir 600 mg / lamivudine 300 mg	emtricitabine 200 mg / tenofovir alafenamide 25 mg
Dosage Level(s)	One tablet per day	One tablet per day	One tablet per day

Route of Administration	Oral	Oral	Oral
Use	Comparator	Background	Background
IMP and NIMP	IMP	IMP where provided centrally; Otherwise dependent on local regulations.	IMP where provided centrally; Otherwise dependent on local regulations.
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor or Locally sourced.	Provided centrally by Sponsor or Locally sourced.
Packaging and Labeling	30 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement

6.2. Preparation/Handling/Storage/Accountability

1. 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.
2. 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.
3. 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).
4. 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 GSK and VH.
- IP accountability will be evaluated using pill counts. This assessment will be conducted during each clinic visit through study completion or early withdrawal. IP accountability records must be maintained throughout the course of the study.
- Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study will use an IVRS/IWRS.

- All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information & directions for the IWRS will be provided to each site
- Study interventions will be dispensed at the study visits summarized in the SOA.
- Returned study intervention should not be re-dispensed to any other participant.

To minimize bias, the dose level of GSK3640254 in each of the treatment arms containing GSK3640254 will be blinded to the research participants and all study personnel during the study. The Sponsor personnel will also remain blinded until the database lock for the Week 24 analysis.

Controlled early access to unblinded PK and PKPD related data will be granted to the designated CPMS vendor contracted to perform the population PK model and any PK review necessary for planned or unplanned safety reviews.

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

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

A participant will be withdrawn if the participant's intervention code is unblinded by the Investigator or treating physician. The primary reason for the discontinuation (the event or condition which led to the unblinding) will be recorded expeditiously in the eCRF.

6.4. Study Intervention Compliance

- When participants are dosed at the site, the date and time of each dose administered in the clinic will be recorded in the source documents.
- When participants self-administer study intervention(s) at home, compliance with study medications will be assessed by direct questioning and review of the diary card during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.
- A record of the number of study medication tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

6.5. Dose Modification

No dose modifications (to doses described in this protocol, or as modified by any IDMC recommendation [see Section 9.5.1]) are allowed in this protocol, including for a decline in Creatinine Clearance.

6.6. Continued Access to Study Intervention after the End of the Study

The study (or a rollover study) is expected to close in the year 2027 at the time GSK3640254 would be expected to be commercially available and/or available in local access programs.

6.7. Treatment of Overdose

Any tablet intake exceeding the randomized daily number of tablets will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. 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.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

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.

Because non-HIV vaccines (e.g. Influenza vaccine or SARS-CoV-2 vaccine) 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 when possible. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment if possible.

DTG should be administered with the following considerations:

- 2 hours before or 6 hours after taking antacid or laxative products or sucralfate containing polyvalent cations (e.g. aluminium and magnesium) or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions, though importantly, Proton Pump Inhibitors are prohibited therapy for any participant in any arm electing to participate in the Stomach substudy.
- Concurrent administration with multivitamins is acceptable. Iron supplements can be taken with study treatment provided that all are taken together with a meal.
- Under fasted conditions, DTG 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 DTG with metformin, to maintain glycemic 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.

6.8.1. Prohibited Medications and Non-Drug Therapies

6.8.1.1. Prohibited Medications: All Participants

The following, general concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered.
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SRM) This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in patients with acute viral hepatitis [James, 2009].

- Proton Pump Inhibitors are prohibited therapy for any participant in any arm electing to participate in the Stomach substudy.

6.8.1.2. Medications that need to be stopped in Screening

The following medications need to be stopped at least 4 weeks prior to the first dose:

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine
- St. John's wort (*Hypericum perforatum*)
- Any other strong CYP3A Inducers (e.g., dexamethasone, rifapentine, rifabutine, etc)
- Fampridine

The following medications need to be stopped at least 2 weeks prior to the first dose:

- Dofetilide and pilsicainide.

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

6.8.1.3. On Treatment Prohibited Medications: GSK3640254 Arms

The following medications may significantly interact with GSK3640254 and are not permitted:

- Strong CYP3A inhibitor (Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole etc);
- Strong CYP3A inducer (e.g. phenobarbital, dexamethasone, carbamazepine, phenytoin, rifampin, rifapentine, rifabutine, St John's wort, etc);
- Substrate of OATP1B3 (e.g. telmisartan, valsartan, olmesartan, rifampin, ezetimibe, statins such as atorvastatin, rosuvastatin, pitavastatin).

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

6.8.1.4. On Treatment Prohibited Medications: When dosing with DTG in any arm

This list applies to the Reference Arm, and to the GSK3640254 Arm once DTG is combined with the optimal dose in the open label Non-Randomised Phase.

- The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, they may not be administered concurrently in participants on the DTG arm.
    - Carbamazepine
    - Oxcarbamazepine
    - Phenobarbital
    - Phenytoin
    - Rifampicin and rifapentine
    - St. John's wort (*Hypericum perforatum*)
    - Fampridine
- Dofetilide and pilsicainide are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity. Any substrate of the OCT2 with a narrow therapeutic window should not be administered concurrently with DTG containing products (see prescribing info).

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Upon study discontinuation, cART should be started, as selected/prescribed/provided by their physician.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will perform an Early Withdrawal visit (see SOA, Section 1.3) and then be evaluated in 2-4 weeks at a Final Follow-up Visit. See the SoA for data to be collected at the time of discontinuation of study intervention.

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

- Confirmed or Suspected Hypersensitivity Reaction;
- Confirmed Virologic Failures as defined in Section 7.1.1;
- Virologic Non-Responder at Week 24, defined as participants who have either:
    - HIV-1 RNA ≥200 c/mL at Week 24, or
    - HIV-1 RNA ≥50 c/mL on repeat testing of Week 24 results and prior to Week 28 (see Figure 1 in Section 4.1.2.2.1)

- If DTG resistance associated mutations (RAM) are detected in viral RNA at Week 4 in participants in the GSK3640254 treatment arms, the participant may continue on study through the Week 48 secondary endpoint BUT may NOT switch over into the open label phase with GSK3640254 Optimal Dose + DTG due to the DTG RAM;
- Participant requires substitution or dose modification of GSK3640254, ABC/3TC, FTC/TAF or DTG;
- Switch of the dual NRTI background (ABC/3TC to FTC/TAF, or vice versa) occurring after the Week 2 visit AND the participant has a last on-treatment HIV-1 RNA ≥50 c/mL;
- Switch of the dual NRTI background (ABC/3TC to FTC/TAF, or vice versa) for a reason other than toxicity management;
- Treatment emergent resistance to any component of the study medications. For participants receiving GSK3640254, the genotypic emergence of an A364V or A364A/V requires discontinuation.
- For participants receiving GSK3640254, a PhenoSense Gag $cFCIC_{50} > 50$ (on-treatment $FCIC_{50}$/Day 1 $FCIC_{50}$);
- Liver toxicity where stopping criteria specified in Section 7.1.2 are met;
- Allergic reaction or Rash criteria as described in Section 10.9.2.1 and Section 10.9.2.2, respectively, are met and no compelling alternate cause is identified;
- Renal toxicity is met and no compelling alternate cause is identified (an estimated GFR of <50mL/min on confirmed measurement as defined in Section 10.9.6);
- Confirmed Proximal Renal Tubule Dysfunction ([PRTD] See Section 10.9.7);
- Pregnancy (intrauterine), regardless of termination status of pregnancy (See Section 8.2.5);
- Diagnosis of Hepatitis B or C viral infection;
- Any clinically significant AE deemed to require discontinuation of the IP;
- Moderate to severe (as clinically determined by the investigator) COVID-19 infection (suspect, probable, or confirmed using the most recent version of the WHO case definition)
- A Grade 4 or related Grade 3 AE: the Investigator will discontinue the participant from the study. If the AE, in the opinion of the investigator, may be representative of gastric toxicity (e.g. obstipation, diarrhea, dysphagia/odynophagia, GI bleeding, mucositis/stomatitis, or nausea), the Investigator may consider performing an evaluation/management plan incorporating elements in the GI Intolerability Evaluation and Management table (Section 8.2.7);
- Any Grade 3 or higher Psychiatric AE. The Investigator will discontinue the participant from the study and arrange for emergency psychiatric evaluation/management; the panel for drugs of abuse will be tested.

- New onset suicidal ideation, as clinically diagnosed by the Investigator (in consultation with psychiatry, if needed). The Investigator will discontinue the participant from the study and arrange for urgent specialist psychiatric evaluation/management.
- Any clinically relevant Grade 4 laboratory abnormalities (with the exception of an asymptomatic grade 4 cholesterol, triglyceride or CPK increase - in the absence of a clinically reasonable explanation);
- Participants who require concomitant medications known to be associated with a prolonged QTc;
- A triplicate set of on-treatment ECGs show the average QTcF >500 msec or increase from baseline QTc >60 msec (See Section 7.1.4);
- If Stomach Substudy Individual Stopping Criteria are met (See Section 4.1.5.2).

7.1.1. Protocol-Defined Virologic Failure

Virologic failure must be confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between two and four weeks after the initial suspected virologic failure sample.

Participants should receive full dose of study treatments across all plasma sampling times used for determining virologic failure.

For the purposes of clinical management in this study, protocol-defined virologic failure (PDVF) is defined as any of the following:

Virologic Non-response

- Decrease from Baseline (Day 1) in plasma HIV-1 RNA of <1.0 log10 c/mL unless plasma HIV-1 RNA is <200 c/mL by Week 12;
- Confirmed plasma HIV-1 RNA levels ≥200 c/mL at or after Week 24 (See Figure 1 and Table 4, Section 4.1.2.2.1);
- Plasma HIV-1 RNA ≥50 c/mL on repeat testing of Week 24 results and prior to Week 28 (see Figure 1 in Section 4.1.2.2.1).

Virologic Rebound

- Confirmed plasma HIV-1 RNA ≥200 c/mL after confirmed consecutive plasma HIV-1 RNA <50 c/mL (see Table 4 in Section 4.1.2.2.1).

Participants who meet the definition of virologic failure must be immediately discontinued from the study.

7.1.1.1. Managing Suspected Virologic Failure/Endpoint Cases

Inadequate adherence is a common cause for virologic failure and should be explored as a first step in management of study participants (e.g., at the first indication of inadequate virologic response or rebound).

All cases that meet a criterion for suspected virologic failure must be confirmed by a second measurement performed at least 2 weeks but not more than 8 weeks (as specified below) apart from the date of the original sample, unless one of the extenuating circumstances outlined below applies.

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as a suspected virologic failure, the Investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of therapy.

The following guidelines should be followed for scheduling confirmatory plasma 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 dose of all IP.
- Confirmatory testing should be scheduled 4 to ~6 weeks (but no more than 8 weeks) following any immunization, during which time the participant should receive full dose(s) of all IP.
- If therapy is interrupted due to non-compliance, or other reasons, confirmatory testing should be scheduled 2 to <4 weeks following resumption of full dose of all IP.
- The participant should have received full dose of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

Sites should contact the study medical monitor to discuss individual participants, whenever necessary.

7.1.1.2. Managing Confirmed Virologic Failure/Endpoint Cases

A participant who meets confirmed virologic failure must be immediately discontinued from the study. Once a participant has been confirmed as meeting the protocol definition of confirmed virologic failure, a sample from the suspected virologic failure visit, and a sample from the Day 1 visit (if not sent previously), will be sent for genotypic and phenotypic resistance testing and the result made known to the Investigator when available.

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 immediately. For all other confirmed virologic failure cases where HIV-1 RNA ≥200 c/mL, resistance testing will be triggered.

If a participant is withdrawn early from participation in the study, the Investigator must make every effort to perform the evaluations outlined in the Schedule of Activities (Section 1.3). These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any participant from the study.

7.1.2. Liver Chemistry Stopping and Increased Monitoring 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). Refer to Appendix 6 in Section 10.6.

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 the algorithm or
- 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 Section can be found in Section 10.6**.**

7.1.2.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.3. Columbia-Suicide Severity Rating Scale

Emergence of any positive (abnormal) response on the C-SSRS, confirmed by the Investigator, during the treatment phase of the study will be cause for immediate clinical assessment of suicidality (by the Investigator or a consulting psychiatrist). Emergence of new onset suicidal ideation or a Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management.

7.1.4. QTc Stopping Criteria

The same QTcF correction formula must be used for each participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

The Baseline QTcF should be based on averaged QTcF values of triplicate ECGs obtained over a brief recording period from the Day 1 pre-dose ECG (see Section 8.2.3).

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. The Investigator's or ViiV Medical Monitor's over-read can supersede that of the machine at any time. If so, it must be noted in the chart.

A randomized participant that develops an on-treatment single ECG QTcF >500 msec or an increase from baseline QTcF >60 msec should have two repeat unscheduled ECG's within 10 minutes apart. Using these three ECGs, if the average QTcF shows either of the following, the participant will be withdrawn from the study (In addition, review of such an ECG with a Cardiologist is encouraged):

- >500 msec, or
- An increase from baseline QTcF >60 msec

Finally, this participant should have 1) a complete, unscheduled chemistry panel, 2) an unscheduled GSK3640254 PK sample, and 3) repeated unscheduled ECGs until their QTc measurement returns to their original averaged QTcF value at Day 1 pre-dose.

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

7.2. Participant Discontinuation/Withdrawal from the Study

- 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, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.3. Lost to Follow Up

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.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (See Section 1.3).
- Please refer to Appendix 11 in Section 10.11 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.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

- Plasma for quantitative HIV-1 RNA will be generated at time points listed in the SOA (see Section 1.3).
- An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 40 c/mL will be used. However, the primary and secondary endpoints will define responders as HIV-1 RNA <50 c/mL.

- Details concerning the handling, labeling and shipping of these samples will be supplied separately.

8.1.1. Lymphocyte Subsets by Flow Cytometry

- Blood samples will be obtained from each participant for the analysis of lymphocyte subsets (CD4 and CD8) by flow cytometry at the timepoints listed in the SOA (Section 1.3).
- Details concerning the handling, labeling and shipping of these samples will be supplied separately.

8.1.2. Disease Progression

- HIV-associated conditions will be recorded as per the SoA (Section 1.3).
- CDC-classification will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (See Section 10.10).

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A targeted physical examination will include, at a minimum, assessments of the skin, lungs, heart, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Investigators should pay special attention to any signs of rash.
- Height and weight will also be measured and recorded. Height will be captured only at Screening; Weight will be captured at each visit to accurately calculate Creatinine Clearance (CrCL) throughout the study.

8.2.2. Vital Signs

- Vital signs will be collected as indicated in the SOA (Section 1.3).
- Vital signs will be measured in a semi-supine position after 5 minutes rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and will include temperature, pulse rate (heart rate), respiratory rate, and systolic and diastolic blood pressure.
    - Blood pressure and pulse measurements will be done with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be recorded in the eCRF where the average of the 2 readings will be calculated.

8.2.3. Cardiac Monitoring with Electrocardiograms

- Triplicate and Single 12-lead ECGs will be obtained as outlined in the SOA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.4 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- Participant should remain still while the tracing is being recorded. Site staff should review the tracing to look for movement artefact and redo the ECG, if necessary.
- The high-quality ECG should be transmitted to the central vendor. If there is an issue with electronic transmission (via analog or LAN), sites will upload the ECG tracing directly in the vendor portal.
- The central vendor will not be providing over-reads on any of the ECGs. The Investigator (or designee) should review the Screening output to determine if any exclusion criteria have been met. Subsequent ECGs should be assessed by the Investigator (or designee) for any new issue or parameter results that meet QTc stopping criteria (See Section 7.1.4). In addition, review of such an ECG with a Cardiologist is encouraged.

8.2.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2 in Section 10.2 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. Please refer to Appendix 11 in Section 10.11 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). 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 11 in Section 10.11 for study management information during the COVID-19 pandemic.
- See Section 10.2 for the list of clinical laboratory tests to be performed and Section 1.3 for the timing and frequency.

- 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 CRF. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, 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 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.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- Refer to the SRM for processing and handling of samples to avoid duplicate and/or additional blood draws.
- All study-required laboratory assessments will be performed by a central laboratory.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF. Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Participants of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 to be eligible for the start of administration of IP.
    - FOR CANADA ONLY: If the Screening Period goes beyond 30 days, a more recent serum test is required. See Footnote 9 to the SoA (Section 1.3) for additional detail.
- Pregnancy testing (urine and/or serum as required by local regulations) will be conducted at Screening, Day 1, and at monthly intervals during study intervention period, as outlined in the SOA (Section 1.3).

8.2.6. Suicidal Ideation and Behaviour Risk Monitoring

The reason for the use of the CSSRS assessment in this study is two-fold:

1. Participants with HIV infection occasionally may present with symptoms of depression and/or other relevant psychiatric diagnoses that increase the risk for suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some participants being treated with INIs, including DTG.
2. GSK3640254 is not a CNS active drug nor is it being developed for a neurologic or psychiatric condition. However, the risk of suicidal ideation was identified with the previous generation MI GSK3532795 at supratherapeutic doses.

Therefore, the use of the CSSRS is appropriate to monitor participants for potential risk of suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior. It is recommended that the investigator promptly referral participants for psychiatric evaluation and management who experience signs of SIB if encountered during the screening period.

If randomized and on-treatment, participants presenting with new onset/treatment emergent depression (e.g. Grade 3-4) should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop because discontinuation of study medication and urgent specialist psychiatric evaluation and management are required (as noted in Section 7.1.3). Independent of psychiatric symptoms, an on-treatment CSSRS will be performed at all study visits. Ultimately, in the event of a new onset suicidality as clinically diagnosed by the Investigator (in consultation with psychiatry, if needed), the participant will discontinue from the trial and the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

Assessment of treatment-emergent suicidality will be clinically diagnosed but monitored during this study using the Columbia Suicidality Severity Rating Scale (eC-SSRS). The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening 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.

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 behavior, 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 GSK/VH within 1 week of the investigator diagnosing a possible suicidality-related AE.

In addition to new onset suicidality, emergent non-suicidal Psychiatric AEs will be evaluated and managed in the following manner:

Any Grade 1 or 2 Psychiatric AE: A Grade 1 or 2 Psychiatric AE may result in additional unscheduled visits (in-clinic or at home) as clinically indicated. This may include a more in-depth assessment of AE through interview, additional unscheduled clinical labs, and/or imaging. Psychiatric consultation may be required at the discretion of the PI/SI. Any pharmacotherapy should be discussed with the ViiV Medical Monitor.

Any Grade 3 or 4 Psychiatric AE: As described in Section 7.1, a Grade 3 or 4 Psychiatric AE will result in discontinuation from the trial and emergency psychiatric evaluation. A urine sample should be submitted for the Drugs of Abuse panel.

8.2.7. GI Intolerability Evaluation & Monitoring Plan (with Stopping Criteria)

Pre-clinical toxicology studies in rats and dogs have suggested a potential for GI related toxicity with GSK3640254. Prior clinical trials have not evaluated for the presence of gastric toxicity in humans. Thus, it is unclear if any of the GI AEs observed in any clinical trial were representative of, associated with, or resulted from gastric toxicity (if present). Thus, in a clinically conservative fashion, this section provides general guidance to the Investigator on the evaluation and management of primarily upper gastrointestinal symptoms (Table 10) irrespective of participation in the optional Stomach substudy. The Investigator may contact the VH Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the trial.

Table 10 GI Intolerability Evaluation and Management

HISTORY	For symptoms of all grades, a thorough history (and differentiation of acute and chronic manifestations) forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical trial.
Abdominal Pain	The Investigator should obtain information on chronology, location, intensity/character, aggravating and alleviating factors, and associated symptoms in the context of the participants relevant past medical history [Millham, 2016]. With chronic symptoms, factors suggestive of an organic process include: fever, night sweats, loss of appetite, weight loss, and nocturnal awakening [Yarze, 2016]. The historical and physical examination should be efficient and lead to an accurate diagnosis soon after presentation.
Nausea and Vomiting	The investigator should attempt to identify the etiology of these symptoms (and whether it is intraperitoneal, extraperitoneal, medication related, infection related, or due to a metabolic disorder [Hasler, 2012].
Dyspepsia	The Investigator should identify the presence of red flags (odynophagia, unexplained weight loss, recurrent vomiting, GI bleeding, jaundice, palpable mass or adenopathy, or family history of GI malignancy). Symptoms of dyspepsia could include early satiety, bloating, or belching. Additionally, atypical symptoms of dyspepsia could include: pharyngitis, asthma, bronchitis, hoarseness, chest pain, or abdominal pain.
Diarrhea	Similar to other GI symptoms, important historical assessment includes duration, onset, pattern, epidemiology (e.g. travel and diet), aggrevating or iatrogenic factors, alleviating factors, stool appearance, presence of other symptoms (e.g. abdominal pain), or weight loss. The differential can be narrowed if there are clear watery, inflammatory, or fatty manifestations [Schiller, 2016].
Other Clinical Syndromes	Additional diagnostic criteria for other GI disorders potentially encountered in the clinical trial are available. [Stanghellini, 2016 and Lacy, 2016]

PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history [Hasler, 2012]. The exam elements may include: ausculatation for bowel sounds (up to 2 minutes if necessary) and palpation (including assessment for rebound, guarding, and muscular rigidity) [Millham, 2016]. Acutely, the investigator may assess for signs of intravascular volume depletion (e.g., orthostasis) and/or aspiration of vomitus as appropriate. Abdominal tenderness and guarding may indicate inflammation. The presence of fecal blood can indicate mucosal damage (e.g., from an ulcer). Complete evaluation of dyspepsia should include an oral examination (poor dentition or pharyngeal erythema) and lungs for wheezing.**
DIAGNOSTIC EVALUATION AND MANAGEMENT	**A major goal in the diagnostic evaluation of a participant with upper GI symptoms is to quickly arrive at a final diagnosis without exposing the participant to unnecessary (invasive) testing; Investigators should exercise good clinical judgment in this regard [Soll, 2009]. A major goal of therapy is directed at correcting the underlying identifiable medical or surgical abnormalities (e.g perforation or infarction) [Malagelada, 2016]. Consultation (eg, gastroenterologist) is recommended as clinically indicated. Emergent action should be taken as necessary: correction of hypovolemia or electrolyte abnormalities.**
Grade 1 symptoms	Participants may be treated symptomatically. If participants develop dyspepsia alone, generally only limited and direct diagnostic testing should be performed. If the participant has dyspepsia, they should limit alcohol, caffeine, chocolate, tobacco, and eating directly before bedtime. Proton Pump Inhibitors are prohibited therapy for any participant in any arm electing to participate in the Stomach substudy.
Grade 2 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): Serum chemistries (for evaluation of fluid and acid/base/metabolic status) and assessment of white blood cells (with differential) and hemoglobin if not recently performed. Amylase and Lipase may also be appropriate. Polymerase chain reaction (PCR) for viruses (e.g., Cytomegalovirus [CMV])

Grade 3 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • CT scan to identify gastrointestinal inflammation • Upper endoscopy with biopsy as indicated (eg, mucosal injury or the presence of red flags). Generally, use of imaging should be appropriate and timely. Management should be targeted at addressing the underlying pathology.
Grade 4 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 and Grade 3 • An acute abdominal series • Focused Assessment with Sonography in Trauma (FAST) Ultrasound Initial management can include correction of hemodynamic and electrolyte abnormalities as clinically indicated. After stabilization, management should be targeted at addressing the underlying pathology.

[a] Grade 4 or related Grade 3 AE: The Investigator will discontinue the participant from the study (see Section 7.1). If the AE, in the opinion of the investigator, may be representative of gastric toxicity (e.g. obstipation, diarrhea, dysphagia/odynophagia, GI bleeding, mucositis/stomatitis, or nausea), the Investigator may consider performing an evaluation/management plan incorporating elements of the above GI Intolerability Evaluation and Management table.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of an AE or SAE can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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 discontinue the study (see Section 7).

Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention 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 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 Section 10.3. 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 information on AEs or SAEs after the conclusion of the study participation. 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.

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 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 Section 10.3.

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. Pregnancy

- Details of all pregnancies in participants will be collected after the start of study intervention and until 35 days after the last dose. Details of pregnancies in partners of participants do not need to be collected in this study.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the participant pregnancy. 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 will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to GSK and VH.
- 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 post-study, pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participant, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 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.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes (HIV-Associated Conditions)

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.10) 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 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 (Section 10.3.2), 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.

If any of the above conditions is met then record the Disease Related Event on either the AE or SAE eCRF page (according to severity) in addition to the HIV Associated

Conditions eCRF page. If categorized as an SAE, report promptly (Section 10.3.5) to GSK and VH.

Additionally, the PI should designate on the eCRF whether or not the AE or SAE meets any aspect of being an AIDS defining condition.

8.3.8. Adverse Event of Special Interest

AEs of special interest (AESIs) include those related to GI intolerability/gastric toxicity, neuropsychiatric safety, QT prolongation and skin and subcutaneous tissue disorders. See Section 8.2.3, Section 8.2.6, Section 8.2.7 and Section 10.9.3 for further details.

8.4. Pharmacokinetics

Only participants who have been randomized to the treatment arms containing GSK3640254 will provide samples for PK analysis.

Subjects will be expected to complete a dosing card with the date and time of IP administration of the last three doses prior to the scheduled clinic visits at which PK is collected (Weeks 4, 8, 12, 24, 36 and 48). These dates and times will be recorded in the eCRF. Additionally, dosing information on the clinic day, including whether or not the dose was administered with food, and the actual date and time of the PK samples must be recorded in the eCRF.

The pre-dose samples **must** be collected within the window of 20-28 hours after the most recent dose taken, with the exception of the 24hr pre-dose collection (the final sample) at Week 2 which has a smaller window of 22-26 hours (see Table 11).

Blood samples will be collected for measurement of plasma concentrations (including but not limited to GSK3640254) at the visits outlined in the SoA (Section 1.3) and as detailed in Table 11.

- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Genetic analyses will not be performed on these plasma samples.
- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Table 11 Pharmacokinetic Sampling Schedule and Related Activities

	Time (Event)	**Window for blood draw**	**Time (Relative to Dosing) Hour: Min**
Intensive PK Subgroup at Week 2 (Day 11-14)	Morning pre-dose work: 20-28 hrs after the dose was taken the day prior: ECGs, vitals and full blood draw to include the pre-dose PK collection[a]		
	Eat Meal **DOSE**[b]**:** Administer study treatment and start the clock for subsequent blood draws.		00:00
	1 hr PK blood draw[c]	± 5 minutes	01:00
	2 hr PK blood draw[c] and ECG[d]	± 10 minutes	02:00
	3 hr PK blood draw[c]	± 10 minutes	03:00
	3.5 hr PK blood draw[c]	± 5 minutes	03:30
	4 hr PK blood draw[c] and ECG[d]	± 5 minutes	04:00
	4.5 hr PK blood draw[c]	± 5 minutes	04:30
	5 hr PK blood draw[c]	± 5 minutes	05:00
	6 hr PK blood draw[c] and ECG[d]	± 10 minutes	06:00
	10 hr PK blood draw[c]	± 1 hour	10:00
	24 hr (morning pre-dose) PK blood draw	± 2 hours	24:00
	Eat Meal and administer study treatment.[b]		
Week 4	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection) *except the post-dose PK tube*[a]		
	Eat meal. Administer dose[b]		00:00
	1 PK sample 2-4hrs post-dose[c]		02:00 – 04:00

	Time (Event)	**Window for blood draw**	**Time (Relative to Dosing) Hour: Min**
Week 8	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection) *except the post-dose PK tube*[a]		00:00
	Eat meal. Administer dose[b]		00:00
	1 PK sample 4.5-8 hrs post-dose[c]		04:30 – 08:00
Week 12	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection) *except the post-dose PK tube*[a]		
	Eat meal. Administer dose[b]		00:00
	ECG 2-6 hrs post dose		02:00 - 06:00
	1 PK sample 8-12 hrs post-dose[c]		08:00 – 12:00
Weeks 24, 36, and 48	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection).[a] There is no post-dose PK collection at these visits.		
	Eat meal. Administer dose[b]		00:00

a) The pre-dose, full morning blood draw and ECG should be done in the standard required sequence of assessments: ECG – Vitals – Blood Draw (all within 15 minutes to ensure that the PK sample from the blood draw approximates that of the ECG).
b) At visits with PK collections, aim to dose the participant near the same time that they have typically been dosing. Best Practice is to plan for approximately 30-45 minutes in which to get these pre-dose assessments and procedures done and the meal consumed by the participant.
c) Each post-dose blood draw should be drawn relative to the time the dose was given; never base the interval for the next blood draw on the time of the previous blood draw
d) For consideration at Week 2 Only: For the subsequent, small blood draws at 2, 4, and 6 hrs during the Intensive PK portion of the visit at Week 2, it is more important that the blood draw be done within the required window of time; attempting to acquire the ECG prior to the blood draw may interfere with that timing. Therefore, the ECG at 2, 4 and 6 hrs can be performed after the blood draw at those time points. The goal is to perform the ECG procedure ±15 minutes of the time point (elapsed from time of dose).

8.5. Genetics and/or Pharmacogenomics

A 6 mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected on Week 8 (or at any time later) from participants who have consented to participate in the genetics analysis (PGX) component of the study. Participation is optional. Participants who do not wish to take part in the genetic research may still participate in the main study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual and the SRM.

8.6. Biomarkers

8.6.1. Serum Biomarkers and [redacted] with Biopsy in the Stomach Substudy

As noted in Section 4.1.5, approximately 7 participants in each of the treatment arms will elect to undergo evaluations with [redacted] with biopsy of the greater and lesser curvatures of the stomach and measurement of Serum Biomarkers to explore the clinical manifestations of gastric toxicity seen in preclinical studies (see Section 2.2.2).

Proton Pump Inhibitors are prohibited therapy for any participant in any arm electing to participate in the Stomach substudy.

These participants will undergo biomarker assessments as follows:

1. Blood collection for the measurement of Serum Biomarkers including Gastrin and Pepsinogen I and II (at minimum: Day 1, Week 24, Week 48, and Week 96).
    - A minimum of 12 hours of fasting is required prior to these collections.
    - Antacids or other medications affecting stomach acidity or gastrointestinal motility should be discontinued, if possible, for at least 48 hours prior to collection.
    - Biotin consumption (also termed as vitamin B7 or B8 ,vitamin H, or coenzyme R) should be discontinued for at least 72 hours prior to the collection of a sample.
    - Esophagogastroduodenoscopy (EGD)
        i. **Planned** biopsies include tissue taken from distinct locations on the greater curvature (2 specimens placed in one specimen cup) and from identified transitional zones on the greater curvature and lesser curvature (2 specimens placed in one specimen cup; see SRM for details). Planned Biopsies will be acquired at Day 1, Week 24 and Week 96, at a minimum.
        ii. **Unplanned** biopsies may be taken, if necessary, based on intra-procedure findings. At the discretion of the endoscopist, tissue samples can be taken from locations other than those planned (see Planned Biopsies above) that represent areas of clinical interest.

Unplanned Biopsies can also be taken at time points other than Day 1, Week 24 and Week 96, if necessary.

2. Examination of Biopsies

- **Unplanned** biopsy samples will be referred to a lab capable to perform immediate processing (standard pathology staining) and diagnosis. Unplanned samples may undergo some of the histological staining described below for the planned biopsies (See SRM for specific details.)

- **Planned** biopsy samples will undergo microscopic examination (H/E, PAS, and Alcian Blue stains [pH 2.5] histochemical stains) by two independent physicians. The following histologic parameters will be assessed (if present): Parietal cell loss, Parietal cell necrosis, Chief cell changes, Foveolar cell hyperplasia, Inflammation, Spasmolytic polypeptide-expressing metaplasia, Intestinal Metaplasia, and Dysplasia. Note, staining for H/E will occur at three levels for each sample; staining for PAS and Alcian Blue will occur at one level for each sample.

  Planned biopsy samples will be processed through paraffin embedded block in real time. However, microtomy, staining and reading/interpretation will occur in batch at a later date; this will maintain precision. Samples from the greater curvature will be evaluated, graded, and documented separately from the samples from the transitional zones on the greater and lesser curvatures.

  Peer review will occur as follows: 1) a physician scientist with surgical fellowship training in research with expertise in Epithelial Biology and Gastric Cancer will read scanned slides virtually (e.g. using the Leica Aperio AT2DX system) and 2) a board-certified pathologist will review the glass slides. Overall, only one interpretation (reflecting agreement between both physicians) will be provided and documented for the greater curvature specimen, and for the transitional zones specimens obtained from the greater and lesser curvature. These findings will provide the basis for individual participant- and study-based stopping criteria (Section 4.1.5.2 and Section 4.1.5.3).

Based upon the totality of these results throughout the study, Immunohisto-chemistry (IHC) may be employed in the future (during or after the study) to further characterize gastric inflammation, metaplasia or abnormal lineages (including but not limited to): MIST1, TFF2, TFF3, CDX2, MUC2, MUC6, GS-II, LECTIN, UEA-1 LECTIN, TGF-a, Ki-67, CD163, CD68 and Pepsinogen.

The frequency of additional CCI monitoring with **planned** biopsies (e.g. Week 48, Week 144, etc.) will be based upon emerging clinical and scientific data solely from this trial; for example, the consistency and histopathologic correlation of Serum Biomarkers, the specific histopathologic findings (if any) on biopsy, etc. Serum Biomarkers (Gastrin, Pepsinogen I and Pepsinogen II will also be collected if/when additional CCI with **planned** biopsies are performed (e.g., Week 144).

Importantly, no formal statistical testing or analysis will be performed for either the GI Biomarkers, the histopathological findings from the greater and lesser curvatures of the stomach, or future IHC of the biopsy samples (should this occur).

8.6.2. Viral Genotyping and Phenotyping Analyses

Some of the plasma samples collected in this study will be used to test for the incidence of treatment emergent genotypic and phenotypic resistance to reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors and the study drug, GSK3640254 maturation inhibitor.

- Samples collected from all participants at Screening will undergo resistance testing just after the samples are collected using the PhenoSense GT assay. As noted in Section 5, a local genotypic resistance assay may be acceptable to the VH study team.

- Samples collected from participants in the GSK3640254 arms at Day 1 and Week 4 will undergo resistance testing just after the samples are collected using the following 5 assays: PhenoSense GT, GeneSeq Integrase, PhenoSense Integrase, PhenoSense Gag assays for GSK3640254, and Gag genotype (using a Next Generation Sequencing platform). This will reveal any early development of resistance with GSK3640254. Testing at this early stage for participants on the DTG reference arm is not necessary, as the resistance profile is already well-described.

- Development of PDVF in any participant will trigger shipment for resistance testing of the sample collected at the time point of interest for the same following 5 assays: PhenoSense GT, GeneSeq Integrase, PhenoSense Integrase, PhenoSense Gag assays for GSK3640254, and Gag genotype (using a Next Generation Sequencing platform).

The resistance assays will be performed at Monogram Biosciences.

Details of the analyses to be performed will be specified in the SAP.

8.6.3. Renal, Bone and Inflammation Biomarkers

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

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.

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
- serum creatinine

Bone biomarkers (blood):

- bone-specific alkaline phosphatase
- procollagen type 1 N-propeptide
- type 1 collagen cross-linked C-telopeptide
- osteocalcin
- 25 hydroxy-Vitamin D

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 CCI [redacted] calculation

8.7. Immunogenicity Assessments

Not Applicable.

8.8. Health Economics/Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study is designed to investigate the antiviral activity, safety, and tolerability of three doses (100 mg, 150 mg, and 200 mg) of GSK3640254 given in combination with either ABC/3TC or FTCF/TAF as compared to the reference treatment (defined as either DTG + ABC/3TC or DTG + FTC/TAF), and to select an optimal GSK3640254 dose for further development. Bayesian analyses will be conducted to evaluate the probability that the

Week 24 response rate, defined as the proportion of participants with plasma HIV-1 RNA <50 c/mL as calculated by the FDA snapshot algorithm, of at least one dose of GSK3640254 has comparable efficacy to the reference treatment using a 10% margin. A positive efficacy decision will be made if any GSK3640254 dose has a high posterior probability (e.g., ≥0.85) of being within the 10% margin.

Posterior distributions of response rates for each dose, *d,* of GSK3640254 and the reference treatment be calculated according to the following Bayesian model where θ_d is equal to the logit of the probability, *p*, of being a responder (plasma HIV-1 RNA <50 c/mL) on arm *d* and follows a normal distribution with mean, μ_d, and variance, σ_d^2.

$$p_d = \frac{e^{\theta_d}}{(1+e^{\theta_d})}$$

$$\theta_d = \ln(\frac{p_d}{1-p_d})$$

$$\theta_d \sim N(\mu_d, \sigma_d^2)$$

The decision to model the logit of θ as normal, rather than a traditional Beta-Binomial model, was made to align with the use of the FACTS (Fixed and Adaptive Clinical Trial Simulator) software. FACTS is the software of choice for evaluating operating characteristics of trials utilizing Bayesian analysis which incorporate adaptive decisions (i.e. early stopping, arm dropping, etc.) The effectiveness of the components of DTG + ABC/3TC as well as DTG + FTC/TAF has been assessed in numerous previous studies, including SPRING 1 [van Lunzen, 2012], SPRING 2 [Raffi, 2013], SINGLE [Walmsley, 2013], and FLAMINGO [Clotet, 2014]. Historical data from these studies suggests that the Week 24 response rate for treatment naïve participants treated with either DTG + ABC/3TC or DTG + FTC/TAF is close to 92%. It is assumed that there will be some differentiation in response rates among doses of GSK3640254.

Bayesian analyses formally incorporate prior beliefs and information about population parameters. The assumptions made will help provide a more reliable estimate when the prior beliefs are combined with the observed data and the prior belief is reasonable. Therefore, the trial will utilize an informative Normal(2.61, 0.7324^2) distribution of the logit of response rate on the reference treatment arm. After inverse logit transformation this distribution has a mean at 0.916 and 2.5 and 97.5 percentiles at 0.765 and 0.982 respectively. This distribution was chosen to mimic a Beta (23,2) distribution which has a mean at 0.92 and 2.5 and 97.5 percentiles at 0.789 and 0.990 respectively. Utilizing a Beta(23,2) prior to estimate the response rate on the reference treatment arm is similar to adding 23 responders and 2 non-responders to the reference treatment arm in the actual study. In the Bayesian framework these two choices of modelling the outcome (normal

logit or Beta-Binomial) should give exchangeable results. A non-informative Normal (0, 5^2) prior distribution will be assumed for the logit of response rate for the GSK3640254 arm.

9.2. Sample Size Determination

Approximately 300 participants will be screened to achieve approximately 150 randomly assigned to study intervention for an estimated total of 40 evaluable participants per GSK3640254 arm and 30 participants on the reference treatment arm. Ideally, 28 participants of the planned sample size of 150 will enrol in the optional Stomach substudy (as described in Section 4.1.5). However, additional participants may be enrolled to ensure adequate sample size of EGD evaluation criteria (See Section 4.1.5.1).

The planned sample size of approximately 40 participants per active arm and approximately 30 participants assigned to the control arm is based on the primary efficacy endpoint of FDA Snapshot response rate at Week 24 (proportion of participants with plasma HIV-1 RNA <50 c/mL). Since the analysis will be conducted using Bayesian methodology, the sample size was determined using robust simulation rather than a closed form equation. The determination of the proposed sample size was guided by two goals of the study: to minimize the probability that a dose with a truly poor response would be selected for further study, and maximize the probability accurately selecting the dose with the highest response rate when there is substantial dose differentiation across arms. Should efficacy be similar across dosing arms, other factors (i.e. safety, tolerability, resistance) will drive the dose selection process. The complete dose selection algorithm will be described in detail in the SAP for the study.

Assuming a response rate of 92% on the reference treatment arm, a 2% separation between each dose of GSK3640254, and a response rate of 80% on the most efficacious dose, the probability of declaring success is approximately 0.167. Conversely, assuming a response rate of 90% on the most efficacious result, the probability of declaring success would be 0.861.

Selected probabilities of making a positive efficacy decision (defined as at least one dose having a posterior probability of being within a 10% margin compared to the reference treatment of at least 0.85), assuming a 2% separation between each dose of GS3640254, are presented in Table 12.

Table 12 Simulated power under various realistic GSK3640254 response rates assuming 2% difference between each dose

Response Rate of most efficacious dose of GSK3640254	80%	82%	85%	87%	90%	92%
Probability of making a positive efficacy decision	0.167	0.265	0.484	0.634	0.861	0.944

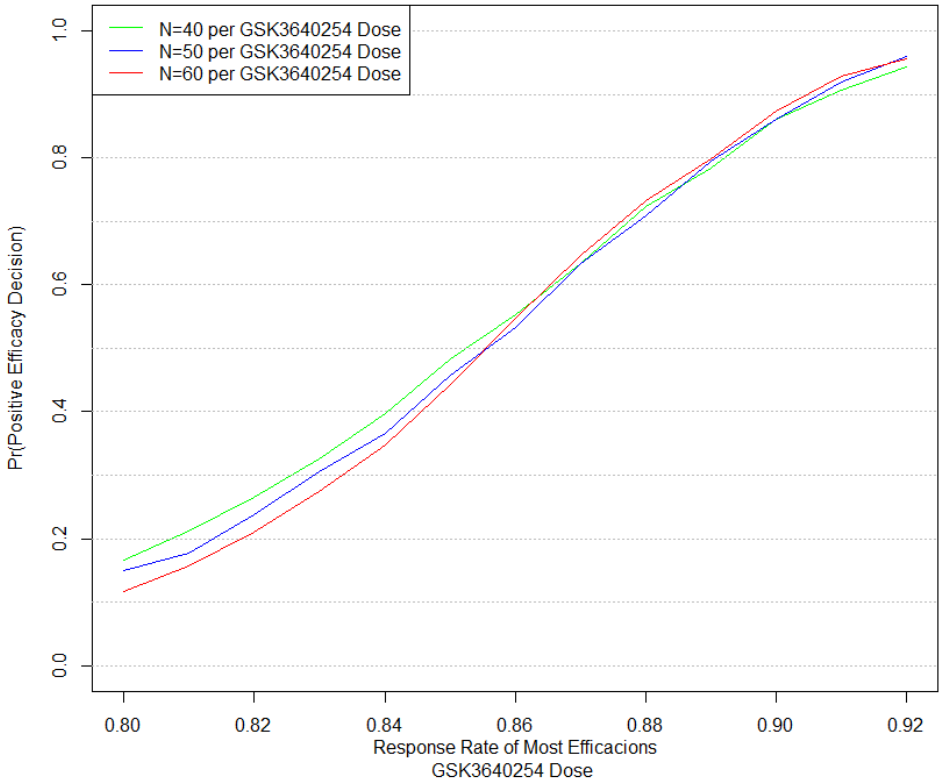
If there is large separation between the most and least efficacious dose, the trial's decision-making criteria will make it unlikely that a dose which is vastly inferior to the

most efficacious dose (10% worse) will be identified as the maximally effective dose. For example, if the three GSK3640254 doses correspond to true response rates of 80%, 85%, and 90% then the probability that the trial will identify each dose as the maximally effective dose is 0.062, 0.219, and 0.719 respectively. These results indicate that the trial has very small chance (< 7%) to select the dose which is truly the least efficacious when there is definitive separation between doses.

9.2.1. Sample Size Sensitivity

To evaluate the study design's sensitivity to sample size, simulations were also conducted using various numbers of participants on the active GSK3640254 doses and the same number of participants (size of 30) for the control arm. Increasing the number of participants enrolled to 50, or 60 participants per dose (compared to the proposed size of 40 per dose) resulted in only modest increases in the probability of correctly making a positive efficacy decision at high response rates (> 90%) and minimal decreases in the probability of incorrectly making a positive efficacy decision at low response rates (< 82%). Figure 3 shows the comparison of decision-making curves for the various sample sizes explored.

Figure 3 Probability of Making a Positive Efficacy Decision at Various Sample Sizes Assuming 2% Difference in Response Rates Between Each Dose



9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

9.3.1. Intent-to-Treat Exposed Population (ITT-E)

The ITT-E population consists of all randomized participants who received at least one dose of study intervention. Participants will be analyzed according to the randomized treatment regardless of what treatment was actually received. Unless stated otherwise, the ITT-E population will be the primary population for efficacy analyses.

9.3.2. Per Protocol Population (PP)

This population will consist of participants in the ITT-E population with the exception of participants with significant protocol violations as defined in the SAP of this study. The PP population will be a secondary population for efficacy purposes.

9.3.3. Pharmacokinetic Population

The pharmacokinetic (PK) population will include all participants who receive GSK3640254, undergo intensive and/or limited/sparse PK sampling during the study, and provide evaluable GSK3640254 plasma concentration data, demographic and baseline characteristics, and/or information on concomitant medications. Participants in this population will be included in the Population PK analysis. A population PK analysis will be done under a separate Population-PK Reporting and Analysis Plan.

See Section 6.3 for details of limited access to these data when the blind must be maintained.

Details of the PK analyses and additional PK populations, if needed, will be provided in the SAP.

9.3.4. Safety Population

The Safety Population consists of all randomized participants who were exposed to study intervention with the exception of any participants with documented evidence of not having consumed any amount of study intervention. Participants will be analyzed according to the actual treatments received. The safety population will be the primary population for safety analyses.

9.3.5. Screened Population

Any participant who signs the ICF is considered to be Screened.

9.3.6. Randomized Population

Any participant who has been randomized (for this study, this means a randomization number was assigned), whether or not the participant ever took a dose of study medication.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Release (DBR) and will include a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy statistical analysis will be based on the proportion of participants in the ITT-E population with plasma HIV-1 RNA <50 copies/mL at Week 24 using the FDA Snapshot algorithm. The posterior distributions of the difference in proportions of participants with plasma HIV-1 RNA <50 copies/mL on each GSK3640254 arm compared with control arm will be produced. Point estimates, Bayesian credible intervals, and frequentist confidence intervals will be derived and displayed. Sensitivity analysis may be performed to assess the impact of the choice of informative prior for control arm. Full details of the planned Bayesian analyses will be provided in the analysis plan.
Secondary	Secondary statistical analyses will be based on the proportion of participants in the ITT-E population with plasma HIV-1 RNA <50 copies/mL at Weeks 48 and 96 using the FDA Snapshot algorithm. Full details will be provided in the statistical analysis plan.
CCI [redacted]	

9.4.2. Safety Analyses

The study is designed to select a dose for further evaluation on the basis of tolerability and virological efficacy in conjunction with immunological response, safety and pharmacokinetic measures. Measures of safety and tolerability will be used to compare the doses in a pre-specified manner will be detailed in the statistical analysis plan of the study. Exposure to study medication, measured by the number of weeks on study drug, will be summarized by treatment arm. The proportion of participants reporting adverse events (AEs) will be tabulated for each treatment arm. 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 from study;
- Incidence of SAEs

Laboratory data, vital signs and ECG data (absolute values and change from baseline) will be summarized by visit and treatment group. More detailed safety analyses will be described in the statistical analysis plan and will be performed on the Safety Population.

9.4.3. Health Outcomes Analyses

The overall proportion of IP study medication taken relative to the planned amount will be estimated via pill counts and summarized by treatment arm for each IP.

Data from C-SSRS assessments will be summarised by visit.

9.4.4. Other Analyses

PK, PK/PD, and biomarker exploratory analyses will be described in the SAP. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

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 SAP; alternatively, a separate SAP 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].

9.5. Interim Analysis

At least four analyses will be performed throughout the course of the study in collaboration with an IDMC as described below:

- An interim analysis will be conducted when data at a pre-specified early timepoint (prior to the Week 24 primary endpoint) is available for a pre-specified percentage of participants. This interim analysis will be conducted to determine if any of the GSK3640254 doses are suboptimal and: 1) should be discontinued from the study or 2) if the entire study should be stopped due to futility. Full details of this analysis are contained in the IDMC charter.

- The primary analysis will be conducted to select an optimal dose when all participants have completed their Week 24 visit

- An analysis will be conducted to confirm the dose selection when all participants have completed their Week 48 visit

- A final confirmatory analysis will be conducted after the last participant reaches Week 96 to characterise the long-term safety, tolerability and durability of antiviral response of all continued doses.

Further data cuts and analyses may be conducted as necessary to support regulatory submissions and publications. No adjustment for multiplicity caused by repeated analysis on the primary endpoint will be made as the interim analysis will be secondary. Type I error rate will not be inflated for the treatment.

The ITT-E population will be the primary efficacy population and the safety population will be the primary safety population for any interim analysis. The actual dosage for participants randomized to a GSK3640254 arm will remain blinded to the sponsor until Week 24 database lock and will remain blinded to investigators and participants until the last participant completes their Week 48 visit.

9.5.1. Independent Data Monitoring Committee

This study will utilize an Independent Data Monitoring Committee (IDMC) to evaluate the efficacy, safety and tolerability of GSK3640254 at early time points in the study. The IDMC will be composed of at least 3 members with at least one member having a medical qualification and at least one member having statistical expertise. The IDMC will review at least one analysis before the primary Week 24 analysis. This review will be used to determine if a recommendation to the CMO and VSLC is warranted to modify study design or conduct including (but not limited to): 1) removing any sub-optimal doses of the GSK3640254 arm from the study or 2) discontinuing the study completely if all GSK3640254 doses are deemed sub-optimal.

If the IDMC recommends discontinuation of one or more arms based on efficacy or safety reasons or both, VH governance board will make a determination to either transition subjects to other arms or to SOC to ensure positive benefit/risk of the study.

In addition, there is an ongoing Phase 2b study in treatment-naïve participants investigating GSK3640254 + DTG (study 212483) that also includes an event triggered (by rate of AE or PDVF) IDMC. If this IDMC were to make a recommendation regarding the discontinuation of any arm in that study, VH governance would determine if/how to incorporate that decision into study 208379 (which may include an independent ad-hoc evaluation by the IDMC for study 208379).

The IDMC charter will contain full details of all summaries and efficacy analyses that will be provided and will be finalized before the first participant is enrolled. To maintain the integrity of the clinical study, only selected staff may be unblinded at interim analyses before all participants have completed Week 24, as deemed necessary by the IDMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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, IB, and other relevant documents (e.g., advertisements, patient-facing materials) 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or to their 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(s).

GSK and VH (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3640254 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3640254 approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participant will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participant 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. Committees Structure

10.1.5.1. Safety Data Review by Safety Review Team and IDMC

- Participant safety will be continuously monitored by the Sponsor's internal safety review committee, which includes safety signal detection at any time during the study
- In addition, an independent safety review by an IDMC for this study is planned prior to the Week 24 primary endpoint. (see Section 9.5.1)
- Case unblinding may be performed for above reviews, if necessary.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of each of the clinical study reports. 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 GSK or VH site or other mutually-agreeable location.
- GSK and VH will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK and VH intend to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- GSK and VH will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK and/or VH Policy.
- GSK and VH intend to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. 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.
- Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Specific Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study data management plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.

10.1.8. 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 and its origin can be found in the Source Data Acknowledgment monitoring form.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first participant Screening that is registered into the IVRS/IWRS is considered the first act of recruitment and will be the study start date.

Study/Site Termination

VH 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 VH. 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 13 will be performed-by the central laboratory with the exception of the test for *H. pylori* that will be done locally by either breath or stool.

Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

Protocol-specific requirements for inclusion or exclusion of participant 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 13 Protocol-Required Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN Amylase, Lipase	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine eGFR/Creatinine Clearance[3]	Sodium, Bicarbonate, and Chloride	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (can be nonfasting; though fasting on days when fasting lipids are collected)	Calcium, Magnesium, and Phosphate Alkaline phosphatase[2]	Creatinine Phosphokinase (CPK)	Fasting Lipid Panel (Cholesterol, Triglycerides, High density lipoprotein [HDL], low density lipoprotein [LDL])

Laboratory Assessments	Parameters
Serum Biomarkers in the Stomach Substudy	• Fasting Gastrin, Pepsinogen I and Pepsinogen II
Renal biomarkers	• Cystatin-C (blood), Retinol Binding Protein (RBP, urine); and Beta-2-Microglobulin (B2M, urine), urine RBP/creatinine ratio, urine B2M/creatinine ratio[3]
Bone biomarkers	• Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin and 25 Hydroxy-Vitamin D[3]
Inflammation biomarkers	• Interleukin-6 (IL-6), High-sensitivity C reactive protein (hs-CRP), D-dimer, Soluble CD14 (sCD14), Soluble CD163 (sCD163)[3]
	• HbA1c and insulin and glucose for CCI [redacted] calculation
Routine Urinalysis	• Albumin • Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy Testing	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for participants of childbearing potential)

Laboratory Assessments	Parameters
Other Tests	• Follicle-stimulating hormone and estradiol • Urine Drug Screen (to include at minimum: amphetamines, barbiturates, cocaine, phencyclidine, opiates, oxycodone, cannabinoids, benzodiazepines, methadone, MDMA, methamphetamines, and tricyclic antidepresants) • *HLA-B*5701* Typing • HIV-1 RNA • CD4+ and CD8+ lymphocyte counts, CD4+/CD8+ cell count ratio • Hepatitis B: hepatitis B virus surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (with reflex to HBV DNA) • Hepatitis C: hepatitis C virus antibody (HCVAb) with reflex to HCV RNA, if positive • Serum albumin • PT/INR • rapid plasma reagin (RPR) • *H. pylori* test by breath or stool (done at local labs)

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6.
2. If alkaline phosphatase is elevated, consider fractionating.
3. 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), 25 Hydroxy-Vitamin D, and HbA1c.

MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, PT/INR = prothrombin time/international normalized ratio, HbA1c = glycated haemoglobin, CCI [redacted] IL-6 = interleukin-6, hs-CRP = high-sensitivity C reactive protein, sCD = soluble CD.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention- intervention 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.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (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 fulfills 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 or significant 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:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF 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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the Sponsor E/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by VH/GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- 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 using the DAIDS Grading Table, Version 2.1, March 2017 https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf and assign it to 1 of the following categories:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life Threatening)
- Grade 5 (Death)

Where a DAIDS toxicity scale is not available for a particular event or parameter, then the investigator will instead make an assessment of intensity using their clinical judgement based on the DAIDS scale.

- NOTE: An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE.

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 Sponsor. 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 Sponsor.**
- 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 Sponsor 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 Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to Sponsor

SAE Reporting to Sponsor via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to Sponsor 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 will capture the SAE Causality in the participant's source notes in a timely manner and the investigator or an appropriately delegated team member will enter the causality into the eCRF. Clinical research associates (CRAs) will monitor the subject source documentation to confirm that SAE causality is being documented by the Investigator in a timely manner. • 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 Sponsor/Medical Monitor Contact Information page.

SAE Reporting to Sponsor via Paper Data Collection Tool
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the M**edical Monitor.** • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Sponsor/Medical Monitor Contact Information page.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Participants of Childbearing Potential (POCBP)

Participants who are female at birth in the following categories are considered POCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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 participants who are female at birth not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Participants who are female at birth on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2. Contraception Guidance

The list does not apply to participants of childbearing potential with same sex partners or for participants of childbearing potential 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.

Methods of contraception are categorized by their effectiveness and user dependency: 1) highly effective methods (failure rate of <1% per year when used consistently and correctly) that have a low user dependency, 2) highly effective methods that are user dependent, and 3) effective methods that are not *highly* effective (failure rate of ≥1% per year when used consistently and correctly, e.g., condoms, cervical cap, diaphragm, sponge).

GSK3640254 and DTG are not genotoxic.

There are no contraceptive requirements for participants who are male at birth based on data for GSK3640254 and the most recent data for DTG.

GSK3640254 has an "unlikely" risk for teratogenicity/fetotoxicity and would allow the use of contraceptive methods both *highly effective* and *effective*. However, DTG has a "possible" risk for teratogenicity/fetotoxicity and appropriate methods of contraception are thus limited to only those methods that are considered to be *highly effective*. Because there is a DTG component in all 4 treatments arms over the course of the study, POCBP will need to adhere to the following highly effective methods of contraception:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE: If a hormonal method is selected, the POCBP is required to be clinically stable on it for at least one month prior to starting treatment in the study.
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[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant 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.* *FOR CANADA ONLY: The partner of a participant who is a POCBP must use a condom with spermicide in combination with any of the methods listed below.*

• 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 *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 participants 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 amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3640254 or HIV and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3640254 or study interventions of this drug class, and HIV. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3640254 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3640254 (or study interventions of this class) or HIV continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If Baseline ALT ≤ 1.5x ULN	
ALT-absolute	ALT ≥ 5X ULN
ALT Increase	NONE for this study.
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
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 ULN OR > 500 U/L (whichever occurs first)
ALT Increase	ALT ≥ 3x baseline but < 5x ULN persists for ≥ 2 weeks (with bilirubin <2x ULN 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 ≥ 2x ULN
Cannot Monitor	ALT ≥ 3x baseline but < 5x ULN 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 treatment.
• Report the event to the medical monitor **within 24 hours**.
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]**.**
• Perform liver event follow up assessments.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** 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.

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 at the central laboratory as described to the right. • A specialist or hepatology consultation is recommended. • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline.	• Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing). • Syphilis screening. • Drugs of abuse screen, including alcohol. Record alcohol use on the liver event CRF • 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. **NOTE: not required in China** • Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4]. • Serum CPK and lactate dehydrogenase (LDH). • 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 CRF 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.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment 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. PK sample may not be required for participants known to be receiving non-ViiV comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. 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**
ALT ≥3x baseline and <5x baseline and bilirubin <2x ULN without symptoms believed to be related to liver injury or hypersensitivity	• Notify the medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return every 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.

Asymptomatic Liver Enzyme Elevations

For asymptomatic subjects who have ALT>3X ULN, following discussions with medical monitor, ALT and other specific lab tests can be repeated in an unscheduled visit. This may include liver panel tests included in study protocol, even though subject did not meet any liver monitoring or liver stopping criteria above.

10.7. Appendix 7: Child-Pugh Classification

A participant is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 14). For participants requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 14 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade[1]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

10.8. Appendix 8: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 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

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, Corrected Version 2.1. [July 2017] is available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

10.9. Appendix 9: 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 10.8). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 10.3.5.

Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study treatment 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 treatment, dosing may continue after discussion with the medical monitor.

Participants who develop a Grade 3 AE that the investigator considers related or possibly related to the study drugs should have study treatment discontinued.

Should the same Grade 3 AE recur within 28 days in the same participant, study treatment should be permanently discontinued, and the participant withdrawn from study. Participants experiencing Grade 3 AEs requiring permanent discontinuation of study treatment 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 drugs.

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 drug if the investigator has compelling evidence that the toxicity is not related to study treatment.

Exceptions are noted for lipid abnormalities (for example, isolated Grade 3 lipid abnormalities do not require withdrawal of IP) and rash in Section 10.9.7.

Grade 4 Toxicity/Adverse Event

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

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study treatment 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 treatment. Exceptions are noted for lipid abnormalities in Section 7.1. An in-clinic Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, and SAEs regardless of attributability and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

Specific Toxicities/Adverse Event Management

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

Participants who permanently discontinue study treatment 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 1.3).

10.9.1. 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 drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 7.1.2 and Section 10.6.

10.9.2. Hypersensitivity Reaction

A well characterized and manageable drug-related HSR is the most important risk associated with ABC. HSR has also been seen with DTG.

10.9.2.1. Reporting of Hypersensitivity Reactions

Subjects may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject 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.

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

Participants receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC hypersensitivity reaction (HSR) and managed appropriately as outlined in the local prescribing information.

10.9.2.2. Abacavir Hypersensitivity Reaction (ABC HSR)

Both ABC and DTG are associated with a risk for hypersensitivity reactions (HSR), and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement. Clinically it is not possible to determine whether a HSR with is caused by ABC or DTG in a combined regimen. HSRs have been observed more commonly with ABC, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for ABC HSR to occur is significantly increased for patients who test positive for the *HLA-B*5701* allele. However, ABC HSRs have been reported at a lower frequency in patients who do not carry this allele. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$) [Mallal, 2008]. In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively [Post, 2010; Squires, 2010].

Investigators must ensure that subjects are fully informed regarding the risk of HSR prior to commencing ABC therapy. Each Subject should also be reminded of the importance of reading the Alert Card accompanying their study medication, and keeping it with them at all times.

The following should be adhered to in the management of Subjects presenting with signs and symptoms suggesting a possible hypersensitivity reaction:

- In any Subject treated with DTG and/or ABC, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making.
- **DTG and/or ABC must be stopped without delay, even in the absence of the HLA-B*5701 allele, if a HSR is suspected. Delay in stopping treatment with after the onset of hypersensitivity may result in a life-threatening reaction.** Clinical status including liver aminotransferases and bilirubin should be monitored.
- Subjects who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining tablets, in order to avoid restarting ABC.
- **After stopping treatment with DTG and/or ABC for reasons of a suspected HSR, DTG and/or ABC or any other medicinal product containing ABC or DTG must never be re-initiated.**
- **Restarting ABC- containing products following a suspected ABC HSR can result in a prompt return of symptoms within hours and may include life-threatening hypotension and death.**

Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH)-E2A definitions of seriousness listed in Section 10.3.2 then, in

addition to reporting the case as an SAE, the ABC HSR CRF should also be completed within one week of the onset of the hypersensitivity reaction.

10.9.3. Rash & Skin Reactions

10.9.3.1. 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 [GlaxoSmithKline Document Number RM2007/00683/13, September 2020].

Participants receiving ABC/3TC NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information.

Skin and Subcutaneous tissue disorders have also been reported across clinical trials with GSK3640254.

Grade 1 Rash: Participants with an isolated Grade 1 rash may continue study drug 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.

Grade 2 Rash: Participants may continue study drug for an isolated Grade 2 rash. However, study drug (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 any systemic signs, allergic symptoms, or if mucosal involvement develops.

Grade 3 Rash: Participants should permanently discontinue study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 rash, except where the aetiology has been definitively diagnosed as NOT attributable to study drug (see below). 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.

Grade 4 Rash: Participants should permanently discontinue study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment). 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 10.8).

10.9.3.2. Skin reactions without other symptoms that are typical of ABC HSR

Including serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or rash with significant liver dysfunction

Participants should be instructed to contact the Investigator as soon as possible if they develop a rash while on study.

Participants who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN and Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the participant should not be re-challenged with any ABC-containing medicinal product (i.e., TRIUMEQ, ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the participant is receiving should also be reviewed and discontinued as appropriate.

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. The index case of hypersensitivity with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including SJS, TEN and erythmea multiforme, have been reported for DTG in clinical trials.

The following guidance is provided for clinical management of subjects who experience rash alone in the absence of accompanying diagnosis of ABC HSR, systemic or allergic symptoms or signs of mucosal or target lesions.

Subjects with an isolated Grade 1 rash may continue IP and background ART at the Investigator’s discretion. The subject should be advised to contact the Investigator immediately if there is any systemic signs, allergic symptoms, or if mucosal involvement develops.

Subjects may continue IP and background ART for an isolated Grade 2 rash. However, IP and background ART (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 (see Section 10.6). The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any systemic signs, allergic symptoms, or if mucosal involvement develops.

Subjects should permanently discontinue IP and background ART (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as adverse events (see Section 10.3) and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings).

If the etiology of the rash can be definitely diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

10.9.4. 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 drug.

10.9.5. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins), physical activity or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study drugs, study treatment should be discontinued, and the participant withdrawn from the study.

10.9.6. 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 and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI cystatin C method [Inker, 2012] should also be done at this confirmatory visit (refer to the SRM for details on the collection and processing of these urine samples). If the creatinine increase is confirmed, the investigator should contact the ViiV Medical Monitor to discuss additional follow-up and medical management.

Participants who experience progression to an estimated GFR (using the CKD-EPI method) [Levey, 2009] of <50 mL/min must return for a confirmatory assessment within

2 weeks. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI cystatin C method [Inker, 2012] should be done at this confirmatory visit (refer to the SRM for details on the collection and processing of these urine samples).

If an estimated GFR of <50 mL/min is confirmed, then study medications should be discontinued and the participant withdrawn.

10.9.7. Proximal Renal Tube Dysfunction

PRTD is defined as:

- Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL;
- Either of the above accompanied by any two of the following:
    - Glycosuria (≥250 mg/dL) in a non-diabetic;
    - Low serum potassium (<3 mEq/L);
    - Low serum bicarbonate (<19 mEq/L).

Participants meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed, participants must be withdrawn from the study.

10.9.8. 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.

Refer to the SRM for details on the collection and processing of urine samples.

10.10. Appendix 10: 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.

10.11. Appendix 11: COVID-19 Pandemic and Clinical Trial Continuity

The COVID-19 pandemic may impact the conduct of clinical studies. Significant logistical challenges may arise from quarantines, variable restrictions on site resource and operations, site closures, travel limitations and the inability of an individual participant to attend clinic visit, interruptions to the supply chain for the investigational product, or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including dispensation of the investigational product to the participant or adhering to protocol-mandated visits and laboratory/diagnostic testing.

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.

This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety, welfare and rights, and to ensure data integrity and 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 for participant management issues that are unrelated to a specific, and documented, impact from COVID-19.

10.11.1. Changes to Study Visits and Study Procedures

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants:

- 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 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 or video app such a Skype, FaceTime, Zoom, etc., where allowed.
  - The assessment should include inquiries to determine if the participant has been impacted by COVID-19 (extent of travel restriction, have they been in contact with any known positive cases [See Section 10.11.5.2 for WHO definition of "contact" - it is important to understand who among our participants could be at risk], assess for COVID-19 as part of the AE/SAE assessment (See Section 10.11.5.2), and inquire about any possibility that the participant has plans to be on an experimental agent for COVID-19 See Section 10.11.4)
  - 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.
  - The CSSRS assessment is already planned to be done via telephone in this study, whether the subject is on site for an in-clinic visit or at home and doing a virtual visit. When the participant is unable to be in the clinic for a required on-site visit, the eCSSRS is still able to be performed at home, preferably prior to virtual contact by the site. Plans for addressing any positive results and referring for care remain no matter from which location the eCSSRS is phoned in.
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.
- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and performance of ECGs. It is the responsibility of the investigator to inform GSK when this occurs and to document in source notes.
- It may become necessary for the Sponsor to broadly incorporate the use of home healthcare staff to perform visits in the participant's home. This possibility is also discussed in the ICF.

- There may be cases where the current 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.

10.11.2. 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.

10.11.3. 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 will 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 will be documented within the main ICF.

- DTP IP should be supplied only in a quantity that is sufficient to cover the interval to the next scheduled dispensation visit. There is a risk that accompanies dispensing more than a single 3-bottles set of blinded GSK3640254. Please see the SRM for details about the limitations with dispensation.
- GSK/VH suggest the use of Marken in most countries for DTP shipments. Otherwise, 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 protocol study treatments 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.

10.11.4. COVID-19 Therapeutic 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.

The protocol does not allow for concurrent enrolment in other interventional studies.

10.11.5. COVID-19 Specific Data Capture

10.11.5.1. Capturing COVID-19 Specific Protocol Deviations

Please refer to the SRM for specific details on capturing protocol deviations as a result of COVID-19.

10.11.5.2. Capturing COVID-19 Specific AEs and SAEs

VH are monitoring the evolving situation with respect to COVID-19 carefully and the impact this may have on ongoing or planned clinical trials. It is important for the study team to describe COVID-19 related adverse events/serious adverse events 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; the most recent definitions should be consulted for each case (WHO). 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 in the setting of clinically defined mild COVID-19 infection.
5. A new COVID-19 infection Case Report Form is included in the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important that the correct information is collected 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.

10.11.5.2.1. WHO Case Definition (December 16, 2020 Version):

Please see the WHO Case Definition for Suspected, Probable or Confirmed case of SARS-CoV-2 infection: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

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.

10.12. Appendix 12: Country-specific requirements

CANADA

A country specific amendment for Canada, 208379/CAN-1, was previously published on 18-SEP-2020 based on a requirement from Health Canada to include a requirement to perform a subsequent serum pregnancy test during Screening if the Screening period extends beyond 30 days – to be collected between Day -7 to Day -5 prior to Day 1.

Text pertaining to this requirement was inserted in these sections:

- Footnote 9 of the Schedule of Activities
- Section 8.2.5, Pregnancy Testing

Additionally, in both sections, additional text regarding both the urine and serum pregnancy testing during Screening and at Day 1 was added for clarity, per request from Health Canada. (This clarifying text was also incorporated into Global Amendment 01.)

PORTUGAL

A country specific amendment for Portugal, 208379/POR-1, was previously published on 18-SEP-2020 based on a requirement from their Central Ethics Committee to explicitly state that participants infected with HIV-2 would be excluded.

A new Exclusion Criterion was added, #41: *HIV-2 infection (either determined by prior testing, medical history, or obtained locally during the Screening window)*

10.13. Appendix 13: Abbreviations and Trademarks

3TC	Lamivudine
ABC	Abacavir
ABC/3TC	Epzicom
ADME	absorption-distribution-metabolism-elimination
AE	Adverse Event
AESI	AE of special interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ART	Anti-retroviral therapy
ARV	Anti-retroviral
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
AUC(0-24)	Area under the plasma concentration time curve from zero to 24
AVB	Atrioventricular block
β-HCG	Human chorionic gonadotropin
BDC	Bile-Duct-Cannulated
BMI	Body mass index
BMS	Bristol-Myers Squibb
bpm	Beats per minute
cART	Combination anti-retroviral therapy
c/mL	Copies per millilitre
C0	Concentration, pre-dose
C24	Concentration, 24 hours post-dose

CAp24	Capsid protein 24
CD4	Cluster of designation 4
CD8	Cluster of designation 8
CDC	Center for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CMO	Chief Medical Officer
CMV	Cytomegalovirus
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CrCl	Creatinine Clearance
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
Ct	Concentration at end of dosing interval
CV	Cardiovascular
CVb	Between-participant coefficient of variation
DAIDS	Division of AIDS
DBR	Database Release
DDI	Drug-Drug Interaction

DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EC90	Effective concentration
EGD	Esophagogastroduodenoscopy
ECG	Electrocardiogram
Emax	Effect, at the maximum
EMEA	European Medicines Agency
EW	Early Withdrawal
FACTS	Fixed and Adaptive Clinical Trial Simulation
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First-time-in-human
Gag	Group-specific antigen
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GSK	GlaxoSmithKline
h or hr	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C antibody
HDPE	High-density polyethylene

HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human immunodeficiency virus-1
HRT	Hormonal replacement therapy
HSR	Hypersensitivity Reaction
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INI	Integrase Inhibitor
INR	International normalized ration
IQ	Inhibitory quotient
IRB	Institutional Review Board
INSTI	Integrase Strand Transfer Inhibitor
IP/IMP	Investigational Product/Investigational Medicinal Product
IRT	Interactive Response Technology
iSRC	Internal Safety Review Committee
ITT	Intent to treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
kDa	Kilodalton
kg	Kilogram
lbs	Pounds
LDL	Low density lipoprotein
LOAEL	Lowest observed adverse effect level

LLOD	Lower limit of detection
LOC	Local Operating Company
MAD	Multiple ascending dose
MedRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Maturation inhibitors
MOA	Mechanisms of action
MSDS	Material Safety Data Sheet
ms, msec	Milliseconds
NOAEL	No-observed-adverse-effect-level
NIMP	Non-investigational Medicinal Product
nM	nanomolar
NPO	nil per os (Nothing by mouth)
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non- Nucleoside Reverse Transcriptase Inhibitor
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
PBAEC90	Protein binding adjusted concentration
PBO	Placebo
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDVF	Protocol Defined Virologic Failure
PI	Principal Investigator
PK	Pharmacokinetic
POC	Proof of Concept

PRSAE	Possible Suicidality-Related AE
PGX	Pharmacogenetics
POCBP	Participant of Childbearing Potential
PONCBP	Participant of Non-Childbearing Potential
PP	Per protocol
PPI	Proton pump inhibitor
PPL	Physician Product Lead
PT/INR	Prothrombin time/International normalized ratio
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
QTL	Quality Tolerance Limit
R	Accumulation ratio
RBC	Red blood cells
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin
SAD	Single ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SI	Sub-Investigator

SOA	Schedule of activities
SOC	System Organ Class
SP1	Spacer peptide 1
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
tlag	Absorption lag time
tmax	Time of occurrence of Cmax
TN	Treatment naïve
ULN	Upper limit of normal
VH	ViiV Healthcare
VLD	Viral load drop
VSLC	ViiV Safety and Labelling Committee
VT	Ventricular Tachycardia
WBC	White blood cells
Wk	Week

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10.14. Appendix 14: Protocol Amendment History

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

Amendment CAN-1 18-SEP-2020

Overall Rationale for the Amendment:

This is a country-specific amendment applicable only to Canada.

To further protect the health and safety of participants who are women of childbearing potential, Health Canada requests to have another serum pregnancy test performed prior to Day 1 if the Screening period extends beyond 30 days. In addition, it was requested to include some clarifying text around both the urine and serum pregnancy testing.

Section # and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities, Footnote 9	Inserted text to require a subsequent serum pregnancy test prior to Day 1 (collected approximately on Day -7 to Day -5) if the Screening period goes beyond 30 days.	This is specific only to Canada, per request.
1.3, Schedule of Activities, Footnote 9 8.2.5, Pregnancy Testing	In both sections, inserted additional text regarding both the urine and serum pregnancy testing during Screening and at Day 1.	These changes were requested for clarity. These will also be included in the next global amendment.

Amendment POR-1 18-SEP-2020

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The Central Ethics Committee requested that the protocol explicitly have an exclusion criterion for participants with concomitant HIV-2 infection.

Section # and Name	Description of Change	Brief Rationale
5.2, Exclusion Criteria	Inserted new exclusion criterion #41 to exclude participants with HIV-2 infection	Portugal Only - CEC request

Amendment 01: 25-SEP-2020

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This is a global amendment.

This amendment was created primarily to replace details of the internal Safety Review Committee to reflect the use instead of an Independent Data Monitoring Committee (IDMC). The decision to switch was based on feedback received from several health authorities and ethics committees, with advice and approval by VH guidance committee. This amendment also includes corrections, clarifications and minor administrative errors.

In addition, details from 2 prior country-specific amendments (Canada amendment CAN-1 and Portugal amendment POR-1) were incorporated into this global amendment.

This document now serves as the current global amendment for all countries.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Objectives and Endpoints, Secondary Safety 3, Objectives and Endpoints, Secondary Safety	Replaced the term “antiviral efficacy” with the words “safety and tolerability”	Error correction
Synopsis, internal Safety Review Committee 4.1, Overall Design 9.5, Interim Analyses 9.5.1, Internal Safety Review Committee 10.1.5.1, Safety Data Review by Safety Review Team and iDMC	Changed all references of an iSRC to IDMC. Provided detail on composition of IDMC and other clarifying text, as well as to make it clear that no employee of Sponsor will have access to the data being reviewed (only in Section 9.5.1).	Based on feedback from several health authorities and ethics committees, and with advice and approval by ViiV Safety and Labelling Committee.

Section # and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities	ECG: Single reading POST dose was noted that the procedure is to be excluded from an EW visit	Error correction
	Fasting Lipids: It was noted that the assessment is to be included at the Final visit or at an EW visit.	For clarity
	Optional Renal, Bone and Inflammatory Biomarkers: Removed the word "optional"	Error Correction
	Inserted new footnote #15 to describe monthly dispensation of the blinded GSK3640254	To help minimize dose administration errors with GSK3640254
1.3, Schedule of Activities, Footnote 9 8.2.5, Pregnancy Testing	Inserted additional text regarding both the urine and serum pregnancy testing during Screening and at Day 1	For clarity
	Inserted a specific statement that pertains to Canada Only, requiring a subsequent serum pregnancy test during the Screening period if the Screening period extends beyond 30 days.	To clarify country-specific requirements for Canada in the body of the protocol to align with Appendix 12
4.1.2.3, Switch to Optimal Dose	Provided detail about the factors that will be considered when assessing participant eligibility to continue into the Non-Randomized Phase of the study.	The detail was missing
5.1, Inclusion Criteria, #6	Inserted a NOTE to provide a statement that there are no contraceptive requirements for male study participants.	For clarity.
5.2, Exclusion Criteria #41	Inserted MDMA and methamphetamines to the list of drugs that will be tested in the	Error correction.

Section # and Name	Description of Change	Brief Rationale
	Drugs of Abuse panel. Inserted a specific Exclusion Criterion #41 that pertains to Portugal Only, requiring participants with HIV-2 infection to be excluded	To clarify country-specific requirements for Portugal in the body of the protocol to align with Appendix 12
6.1, Study Intervention(s) Administered	For the Randomised Phase, Arm 2, indicated that the Use of GSK3640254 25mg tablets is Experimental, not Placebo	Error Correction
7.1.4, QTc Stopping Criteria 8.2.3, Cardiac Monitoring with Electrocardiograms	Inserted guidance for site to consult with a cardiologist if the ECG output shows QTc stopping criteria have been met	To confirm participant should be discontinued
8.3.5, Pregnancy	Removed incorrect information from bullet 2, and removed bullet 4 – both containing incorrect information that directly conflicted with correct information in bullet 1. Reporting of partner pregnancies is not required.	Error Correction
8.6.1, Serum Biomarkers and EGD with Biopsy in the Stomach Substudy 10.2, Appendix 2, Table 13, Protocol Required Safety Laboratory Tests	Removed the measurement of gastric pH	Assessment cannot be performed using EGD as planned
9.1, Statistical Hypothesis	Inserted a superscripted 2 at two values: 0.7324 and 5 Inserted logit text	To clarify that 0.7324 and 5 are the standard deviations not variances To clarify that the normal distribution represents the logit of response rate instead of the actual response rate
9.2, Sample Size Determination	Changed “non-inferiority margin” to “margin”	To emphasize that this is not a formal powered non-inferiority study
9.3.4, Safety Population	Removed 3rd row of table, as the Safety Population is already described in the preceding text	Removed redundancy

Section # and Name	Description of Change	Brief Rationale
10.2, Appendix 2, Table 13, Protocol Required Safety Laboratory Tests	Removed the word "Safety" from the table title as the table includes parameters for many purposes, not just safety. Removed Cystatin C from the standard clinical chemistry assessments; it is only done as part of the Biomarker assessments as outlined in a subsequent row. Added MDMA and methamphetamines to the Urine Drug Screen in "Other tests."	Error corrections.
10.4.2, Contraceptive Guidance	Inserted information that there are no contraceptive requirements for male study participants based on data for both GSK3640254 and the most recent data for DTG. Removed footnote c and its corresponding guidance on the use of male condoms	For clarity, as the protocol did not previously include a specific statement that contraceptive measures were not required for male study participants. Error correction
10.12, Appendix 12, Country-specific requirements	Added new sections to describe previous country specific amendments for Canada (CAN-1) and Portugal (POR-1) that will now be incorporated into this global amendment.	To provide clarity on past country-specific amendments (CAN-1 and POR-1) that have been published prior to this amendment and are consolidated into this global amendment
10.13, Abbreviations and Trademarks	Inserted new abbreviations used in this amendment	For reader's reference
Section 10.14, Appendix 14: Protocol Amendment History	Updated to incorporate changes from previous amendments	To reflect current status of amendments
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 1/SS-1 (244689): 11-DEC-2020

Overall Rationale for the Amendment:

This is a site-specific amendment applicable only to Site 244689 in South Africa.

To further protect the health and safety of participants, the ethics committee at the University of Cape Town, Site 244689, requests to modify the existing Exclusion Criterion #13 to further exclude participants with a familial history of sudden cardiac death. The EC believes that prolonged QT may be undiagnosed, especially in resource-constrained settings, and knowledge of a familial or personal history of long QT syndrome may not be available.

Section # and Name	Description of Change	Brief Rationale
5.2, Exclusion Criteria, #13	The existing exclusion criterion was modified to further exclude participants who have a familial history of sudden cardiac death.	This is specific only to Site 244689 in South Africa, per EC request,

Amendment 02: 09-APR-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This is a global amendment.

This amendment was created primarily to make non-substantial changes generally related to inclusion/exclusion criteria and the screening period, esophagogastroduodenoscopy (EGD) biopsy-based stopping criteria for individual participants and the study overall. The other changes exist for further detail, clarity, and current information.

Section # and Name	Description of Change	Brief Rationale
1.1, Synopsis, Overall Design	Inserted text to address the eradication of *Helicobacter pylori*	For accuracy given that this protocol amendment will allow for eradicating and retesting of *Helicobacter pylori* within a single screening period.
1.3, Schedule of Activities Screening	Inserted detail that the 42-day Screening Period may be extended (delaying	For consistency with the allowance for the Stomach

Section # and Name	Description of Change	Brief Rationale
	Randomization) to a maximum of 63 days in certain circumstances	Substudy
Week 2	Inserted Day 11-14 window for the Week 2 visit	For clarity
Electrocardiograms (ECGs)	Included windows of ± 15 minutes for post-dose ECGs	Detail was missing.
Optional Stomach Substudy	Provided detail that the Day 1 CCI needs to be done during the Screening Period, while the Day 1 substudy Biomarkers are drawn at the Day 1 visit.	For clarity
Pharmacokinetic (PK) – Sparse, PK-Intensive	Provided reminders that there are separate PK lab kits for Week 2 (Intensive PK), and Weeks 4, 8, 12, 24, 36 and 48 (Sparse PK). At any visit where PK is to be collected, sites will use BOTH the regular lab kit for the visit AND the PK lab kit for that visit. The PK lab kit contains a pre-dose PK tube that sites need to collect pre-dose along with all of the other pre-dose labs in the regular lab kit.	To ensure successful, proper PK collection.
Footnote #6	Removed text that indicates any positive response on the CSSRS would result in exclusion.	To allow for increased clinical judgment into patient eligibility for trial (note: CSSRS is still being used during screening)
1.3, Schedule of Activities (Pregnancy Test, Footnote 9); 2.3.1, Risk Assessment 4.1.2.2.2, Virtual Visits; 5.1, Inclusion Criteria (#6 – made #7 by this amendment); 5.3.2, Alcohol, Tobacco and Marijuana; 8.2.5, Pregnancy Testing;	Changed all references of WOCBP (women of childbearing potential) to POCBP (participants of childbearing potential) and changed all references of "women/female" to "participants who are assigned female at birth"; references to males were changed to "participants who are assigned male at birth".	To acknowledge gender diversity and gender fluidity

Section # and Name	Description of Change	Brief Rationale
8.3.5, Pregnancy; 10.4 1, Appendix 4, Contraceptive and Barrier Guidance, Definitions 10.4.2, Contraceptive Guidance		
2, Introduction, 3rd paragraph 1.1, Synopsis	Updated information about the GSK3640254 program	To align with current information
2.2.3, Key Clinical Data on GSK3640254 to date	Updated information in 2nd, 4th and 5th bullets Removed 6th bullet	To align with current results summaries
2.2.4, Key Phase 2a (208132) Clinical Data on GSK3640254	Removed the word "Preliminary" from the section title; Updated text with more current information; Updated Table 1 and Table 3 with final data. Replaced Table 2 with final data.	To align with current information
2.3.1, Risk Assessment	Updated most categories with current information.	To align with current information
4.1.1, Screening Period	Indicated that the Screening Period may be extended up to a maximum of 63 in certain circumstances (no longer uniquely for stomach substudy participation).	For consistency.
4.1.2, Treatment Period	Added timing information for the Week 2 Visit (to be performed Day 11-14)	For clarity, and to be consistent with updates made in 4.1.2.1.1
4.1.2.1.1, Optional Intensive PK Portion of Week 2 Visit – GSK3640254 Arms Only	Updated the timing of Week 2 visit from Day 9-14 to Day 11-14.	Day 11 is a more appropriate start of the window, considering the viral load interest at the visit.
4.1.2.2.1, Virologic Management Figure 1 Table 4, footnote d	Changed instruction for Week 24 Non-Responders – who must discontinue immediately from the study;	For safety

Section # and Name	Description of Change	Brief Rationale
Table 4	Inserted bullets where needed	For clarity and ease for the reader
4.1.3, Follow-up	Inserted instructional text regarding required follow-up work on participants at the end of the study.	Detail was missing
4.1.4, Study Completion	Moved text better suited for Section 4.1.3.	For clarity
4.1.5, Optional Stomach Substudy, (EGD with Biopsy and Serum Biomarkers)	Provided detail that the Day 1 EGD needs to be done during the Screening Period, while the Day 1 substudy Biomarkers are drawn at the Day 1 visit; Retracted statement that the GI Physician must be recorded as a co-Investigator /Sub-Investigator and indicated that this should be the case only where locally allowed.	For clarity To defer to local regulations
4.1.5.2, Stomach Substudy Criteria for Stopping an Individual Participant		Ensure participant safety
4.1.5.3, Stomach Substudy Criteria for Stopping the Study	To date, criteria for stopping an individual participant or the study overall based upon EGD findings (e.g. histopathology of the greater curvature and lesser curvature) were not in the protocol – but clearly stated as a topic for a future amendment. In this amendment, the criteria have been added	Ensures participant safety.
5, Study Population	Provided mitigations for the Screening period when results are delayed. 1: Screening period may be extended 2: When Monogram Biosciences cannot report the PhenoSenseGT in a timely manner and a participant has to be rescreened, the	To minimize delays in treating participants

Section # and Name	Description of Change	Brief Rationale
	Monogram test results from the initial Screening period may be used to determine eligibility in the subsequent Screening period. 3: There may be cases where ViiV Healthcare (VH) will allow the use of local resistance labs to be used to determine eligibility only after review of the local lab test with VH responsible staff. Inserted clarifying text for Retesting in a single Screening period.	
5.1, Inclusion Criteria #4 1.1, Synopsis	Modified the CD4 count needed to meet eligibility from 350 to 300	Based upon early recruitment data through March 2021, the Sponsor is slightly lowering the CD4 T-cell count inclusion criteria to improve eligibility/recruitment without compromising safety.
#5	Inserted new Inclusion Criterion #5, requiring antiviral susceptibility to the selected Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone Inclusion criteria #5-#8 subsequently shifted to become #6-#9	To meet request made by Health Authority Review
5.2, Exclusion Criteria #7	Removed unnecessary text related to allergy or sensitivity to the study drugs or drugs in the same class as that information would not be known to those who are treatment-naive	For accuracy
# 8	Provided the Investigator with the ability to make a full clinical assessment of the participant's psychiatric fitness, in combination with output from the eCSSRS.	To make this eligibility assessment more clinically appropriate

Section # and Name	Description of Change	Brief Rationale
#13	Inserted text to allow cardiac death to be assessed, because in some cases, there may not be any personal or familial historical record of prolonged QT	To allow for a secondary way to assess personal or familial cardiac risk; This also aligns the global protocol with a site-specific request (2019N399207-04)
#21, #22, #30 and #37	Included current information relative to SARS CoV-2	To align with the treatment options now available during the global pandemic
#23	Removed distinct mutations specific to study treatments in lieu of using the simple statement that resistance to the selected backbone would meet exclusion	To meet request made by Health Authority Review
#26	Clarified that total bilirubin is the parameter to be assessed for bilirubin	To align with the laboratory parameters as they are reported
#27	Indicated HBV DNA testing will be done on reflex	To align with study central lab practices
#29	Indicated the parameters within which Helicobacter pylori can be eradicated, and retested within a single screening period	To align with guidance [Chey, 2017]
#31	Provided the parameters within which syphilis can be treated relative to Screening or Day 1.	To align with internal VH guidance
#36	Reduced the length of time during which a max amount of blood or blood products can be donated	To better align with protocol visit intervals
#39	Removed the criterion that excluded anyone with any positive response on the CSSRS	To align with text now in Exclusion Criterion #8
#40 (made #39 by this amendment)	Corrected the lower bound for heart rate that may be rechecked - from 100 to 101	For accuracy
5.3.1, Meals and Dietary	Included text guidance for content of a low-fat meal	For ease of the reader

Section # and Name	Description of Change	Brief Rationale
Restrictions	(found in the FDA Draft Guidance [2017] already listed in References, Section 11). Removed restrictions with certain citrus fruits and juices and red wine.	To align with decisions made within the program.
5.5, Criteria for Temporarily Delaying Randomization; 5.5.2, Delaying Randomization, Other; 5.5.3, Contemporary lab result	Described when and how randomization may be delayed/screening period may be extended.	To align with new protocol strategies to improve eligibility/recruitment without compromising safety
6.5, Dose Modifications	Clarified information regarding dose modifications which are not allowed	For accuracy
6.8, Concomitant Therapy	Provided an allowance for the possibility of the use of certain SAR CoV-2 vaccines	To align with the treatment options now available during the global pandemic
6.8.1.4, On Treatment Prohibited Medications: When dosing with DTG in any arm	Indicated that any substrate of the OCT2 with a narrow therapeutic window should not be administered concurrently with DTG-containing products	For accuracy.
7.1.1, Protocol –Defined Virologic Failure	Removed information that is no longer applicable	For accuracy
7.1.1.2, Managing Confirmed Virologic Failure/Endpoint Cases	Provided information that resistance testing will not be performed on samples with a HIV-1 RNA too low for the resistance testing to be successful	To eliminate unnecessary and futile testing
8.2.3, Cardiac Monitoring with Electrocardiograms	Corrected information for the actual practice of actions needed when electronic transmission methods for ECG have failed	For accuracy
8.2.6, Suicidal Ideation and Behaviour Risk Monitoring	Removed text that would not actually be put into practice	For accuracy
8.3.5, Pregnancy	Inserted information about the use of the Antiretroviral	To align with VH practice of

Section # and Name	Description of Change	Brief Rationale
	Pregnancy Registry	voluntarily reporting pregnancies
8.3.7, Disease-Related Events and/or Disease-Related Outcomes (HIV-Associated Conditions)	Modified section title Provided instruction when recording AEs and SAEs that are AIDS-defining conditions	For appropriateness. To align with eCRF completion requirements
8.3.8, Adverse Events of Special Interest	Inserted this new section to address the risks as having special interest	To align with compound-related risks
8.4, Pharmacokinetics, Table 11	Modified Week 2 visit timeframe Added windows for the timing of post-dose ECG to the table footnote	For accuracy
8.6.1, Serum Biomarkers and CCI with Biopsy in the Stomach Substudy	Provided text to describe that much detail can now be found in the SRM. Defined Planned vs, Unplanned biopsies	For clarity
8.6.2, Viral Genotyping and Phenotyping Analyses	Inserted text to indicate that local resistance results may be considered to determine eligibility.	To align with new protocol strategies to improve eligibility/recruitment without compromising safety
9.5.1, Independent Data Monitoring Committee 1.1, Synopsis	Provided detail about actions VH may take based on IDMC recommendations; Provided detail about some effect the analyses/timing in a concurrent study may have on 208379.	For clarity.
10.1.7, Data Quality Assurance, 6th bullet	Provided information that detail can be found in the study data management plan	For information only
10.2, Appendix 2: Clinical Laboratory Tests	Corrected detail about Routine Urinalysis Inserted testing for Creatinine Phosphokinase to the Clinical Chemistry panel	For accuracy

Section # and Name	Description of Change	Brief Rationale
10.3.4, Recording and Follow-Up of AE and SAE	Simplified the definition of the Intensity grades.	To simplify.
10.4.2, Contraceptive Guidance	Inserted a detail that is specific to Canada, as found in the Canada-specific amendment	To bring alignment of prior amendments into this one document moving forward.
10.6, Appendix 6: Liver Safety Required Actions and Follow-up Assessments	Removed information regarding rechallenge or treatment restart. Included some additional follow up assessments to be performed.	To clarify that study drug must be stopped immediately when ALT ≥ 5X ULN and that restart is not permitted For accuracy.
10.9, Appendix 9: Toxicity Management	Removed text that described treatment interruptions, which are not allowed in this protocol. Inserted a detail that SAEs are to be followed into the post-dosing follow-up period, regardless of attributability	For accuracy For accuracy
10.9.2.2, Abacavir Hypersensitivity Reaction	Removed language that allowed a possible restart of DTG or ABC	To mitigate treatment emergent resistance
10.9.3.1, Rash 10.9.3.2, Skin reactions without other symptoms that are typical of ABC HSR	Modified actions to be taken with Grade 1 and/or Grade 2 rash.	For safety.
10.11.4, COVID-19 Experimental Agents	Defined the allowable vaccinations	To be aligned with current SARS CoV-2 pandemic guidance
10.11.5.2.1, WHO Case Definition	Removed outdated text and provided hyperlink to updated WHO Case definitions	Updates became available
10.13, Appendix 13, Abbreviations and Trademarks	Updated abbreviations, as needed, based on other amendment changes	For accuracy
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 03: 10-MAY-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment:

Study 208379 is undergoing this substantial amendment to reduce the sample size from approximately 210 participants to approximately 150 participants. This reduction of 60 participants will occur equally among the 3 experimental arms. There is no change to the Dolutegravir (DTG) reference arm. Thus, the number of participants will be as follows (each arm in combination with open-label Nucleoside Reverse Transcriptase Inhibitor [NRTI] backbone as originally described):

Arm	Original Number of Participants	Amended Number of Participants
GSK3640254 100 mg	60	40
GSK3640254 150 mg	60	40
GSK3640254 200 mg	60	40
DTG	30	30
Total	210	150

The justification of this reduction in sample size is as follows:

1) Since the trial began screening in November in 2020, approximately 89% of sites world-wide have been activated. The Sponsor anticipated screening would complete by 18 May 2021. However, at the time of this substantial amendment approximately 109 participants have been screened and approximately 22 have been randomized. The reasons for slower than anticipated recruitment are based upon the multi-factorial impact of the global Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) pandemic. Qualitative feedback from Investigators shows the incidence of known newly diagnosed Human immunodeficiency virus-1 (HIV-1) infection has decreased. Moreover, physicians and newly infected patients have a strong desire to immediately start antiretroviral therapy so they are less likely to participate in this Phase 2b study which has a screening period of approximately 42 days.
2) The Sponsor does not have formal statistical testing in this trial. Note, Section 9 has been updated to describe modifications to the Statistical Considerations. The Sponsor finds the changes Type I error rate and Power to be clinically acceptable.
3) A reduction in sample size does not limit the ability to make clinical inferences on the efficacy, safety/tolerability, and resistance of an optimal dose GSK3640254 (for subsequent clinical development) – resulting in maintenance of clinical integrity and unchanged risk benefit ratio to study participants.
4) Of the approximately 109 participants screened, a screening Phenosense GT result is available for 22 participants. Of the 22 participants, there is ample diversity in HIV-1 sub-type as follows: Sub-type B (13 participants), Sub-type C (2

participants), and 1 participant in each of the following Sub-types: Complex, AG, G, B/G, F1, AE, A1. Thus, a smaller sample size would not limit diversity in HIV-1 sub-type. Preserving the diversity of HIV-1 sub-type still allows the Sponsor to evaluate the broad spectrum of efficacy of GSK3640254 (note: Gag polymorphisms, varying by sub-type, impacted prior developmental Maturation Inhibitors).

CCI [redacted]

6) The Sponsor will conduct a new Phase 2b study (Study 212483 anticipated to start in July 2021) – also in treatment naïve adults – investigating GSK3640254 (at the same 3 doses) in combination with DTG. The experimental sample size in those arms will be 30 in each arm (90 total). Combined, a robust Phase 2b data set will still be generated enabling a Phase 3 program; specifically, approximately 120 and 90 treatment naïve adults, will be randomized to an experimental arm containing GSK3640254 in this trial and Study 212483, respectively.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Overall Design, Brief Summary, Number of Participants Section 4.1, Overall Design Section 4.1.1, Screening Period Section 4.1.5.1, Stomach Substudy Enrollment Considerations Section 9.2, Sample Size Determination	Number of total participants in the study was reduced from 210 to 150	See the *Overall Rationale for the Amendment* described above.
Synopsis, Number of Participants Section 1.2, Schema Section 4.1.2.1, Day 1 through Week 24 Section 9.2 Sample Size Determination Section 9.2.1, Sample Size Sensitivity	Number of participants in each of the GSK3640254 treatment arms was reduced from 60 to 40	See the *Overall Rationale for the Amendment* described above.
Section 4.1.2, Treatment Period	Corrected the protocol section number in paragraph 8 in reference to the Optional Intensive PK portion of the Week 2 visit	For accuracy
Section 5.2, Exclusion Criteria, #21 (Note) and #31 (Note)	More appropriate word choices were made	For accuracy when translating the documents into other languages
Section 6.6, Continued Access to Study Intervention after the End of the Study	Corrected the GSK compound number	For accuracy
Section 9.2 Sample Size Determination (Table 12 and related text)	Recalculations were done for Type I error and Power.	Required due to the reduction in total number of participants and reduction in number of participants in each GSK3640254 arm.
Section 9.2.1, Sample Size Sensitivity (and Figure 3)	Updated due to change in sample size	Required due to the reduction in total number of participants and reduction in number of participants in each GSK3640254 arm.

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