TITLE PAGE

Protocol Title: An Open-Label One-way Interaction Clinical Trial to Evaluate the Pharmacokinetic Interactions Between GSK3640254 and Tenofovir Alafenamide/Emtricitabine in Healthy Subjects

Protocol Number: 208134

Compound Number: GSK3640254

Study Phase: Phase I

Short Title: Study to Evaluate the Effect of GSK3640254 on the PK of Tenofovir Alafenamide/Emtricitabine

US IND Sponsor Name and Legal Registered Address:

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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. PPD with GlaxoSmithKline are supporting ViiV Healthcare in the conduct of this study.

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

Regulatory Agency Identifying Number(s):
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SPONSOR SIGNATORY:

PPD

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Open-Label One-way Interaction Clinical Trial to Evaluate the Pharmacokinetic Interactions Between GSK3640254 and Tenofovir Alafenamide/Emtricitabine in Healthy Subjects

Short Title: Study to Evaluate the Effect of GSK3640254 on the PK of Tenofovir Alafenamide/Emtricitabine

Rationale: This is an open-label, single-sequence, one-way drug interaction study to investigate the effect of GSK3640254 on the pharmacokinetics (PK) of tenofovir alafenamide (TAF) and emtricitabine (FTC). Treatment of human immunodeficiency virus (HIV) infection frequently involves combination therapy. It is important to understand any interactions and resulting changes in exposure (if any) when HIV medications are given in combination. Data from this study will contribute to dosing recommendations when GSK3640254 and TAF/FTC are given in combination.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess the effect of GSK3640254 on the PK of TAF, FTC, and the active metabolite of TAF prodrug, TFV under fed conditions in healthy participants	• AUC(0-τ) and Cmax for TAF • AUC(0-τ), Cmax, and Cτ for FTC and TFV
Secondary	
• To assess the safety and tolerability of TAF/FTC administered alone and when coadministered with GSK3640254 in healthy participants	• Safety and tolerability parameters for AEs/SAEs, observed and change from baseline clinical laboratory assessments, ECGs, and vital sign measurements
• To characterize the steady-state PK of GSK3640254 in the presence of TAF/FTC in healthy participants	• AUC(0-τ), Cmax, Cτ, and Tmax for GSK3640254
• To characterize the steady-state PK of TAF, FTC, and TFV alone and in combination with GSK3640254 in healthy participants	• Tmax for TAF, FTC, and TFV

AE = adverse event; AUC (0-τ) = area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state; Cmax = maximum observed concentration; Cτ = Plasma concentration at the end of the dosing interval; ECG = electrocardiogram; FTC = emtricitabine; PK = pharmacokinetics; SAE = serious adverse event; TAF = tenofovir alafenamide; TFV = tenofovir; Tmax = time of maximum observed concentration.

Overall Design: This is a Phase 1, open-label, fixed-sequence 2-period, one-way drug interaction study designed to assess the pharmacokinetics (PK), safety, and tolerability of GSK3640254 and TAF/FTC when administered alone and in combination in healthy participants.

The study will consist of a screening period and 2 sequential treatment periods. Participants will be screened with 28 days before the first dose of study intervention.

There is no washout between the last dose of study intervention in Period 1 and initiation of study intervention in Period 2. The participants will fast overnight for at least 8 hours prior to dosing and will receive the moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Pharmacokinetic blood samples for analysis of TAF, FTC, and TFV will be collected before dosing (0 hour) on Days 2 through 14 (Period 1) and Days 1 through 7 (Period 2) and up to 24 hours after TAF/FTC dosing on Period 1, Day 14 and Period 2, Day 7. Pharmacokinetic blood samples for analysis of GSK3640254 will be collected before dosing (0 hour) on Days 2 through 7 (Period 2) and up to 24 hours after GSK3640254 dosing on Day 7.

Safety and tolerability will be assessed by monitoring and recording of adverse events, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram results, and physical examination findings.

Study assessments will be performed as indicated in the Schedule of Activities. Participants will be confined to the clinic from Day –1 until discharge on Period 2, Day 10.

Disclosure Statement: This is a single group, single arm study that has no masking.

Number of Participants: Approximately 16 participants will be treated to ensure that 12 evaluable participants complete the study.

Intervention Groups and Duration: The treatments will be as follows:

- Treatment A: TAF/FTC 25/200 mg once daily (QD) on Days 1 through 14 (Period 1)
- Treatment B: TAF/FTC 25/200 mg QD coadministered with GSK3640254 200 mg QD on Days 1 through 7 (Period 2)

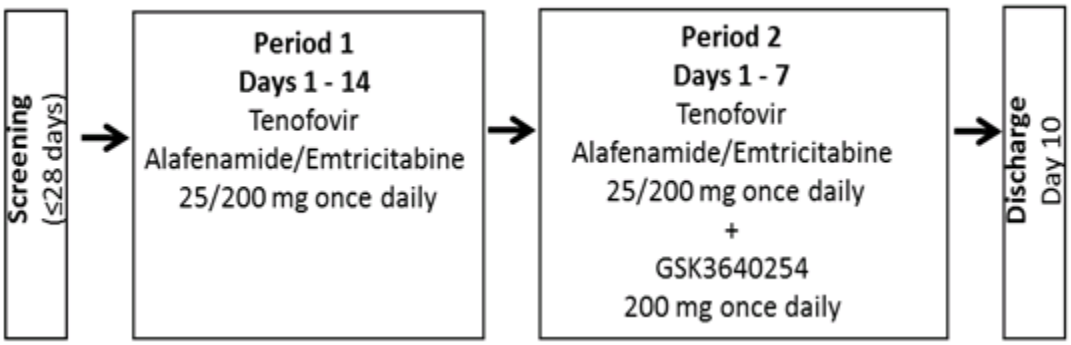
The duration of the study, including Screening, is approximately 52 days.

Data Monitoring Committee: No

1.2. Schema

A summary of the overall study design is presented in Figure 1.

Figure 1 Study Design Schematic



1.3. Schedule of Activities (SoA)

- Screening procedures may be done over more than 1 visit but must all be completed within 28 days prior to the first dose of study intervention.
- The following demographic parameters will be captured: year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria.

Screening Visit

Procedure	Screening (up to 28 days before Day 1)
Outpatient visit	X
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight [1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
12-lead electrocardiogram (ECG)	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X
Serum pregnancy test	X
Follicle-stimulating hormone (FSH) (as needed, to confirm postmenopausal status)	X
Drug, alcohol, and cotinine screen	X
HIV, Hepatitis B and C screening	X

HIV = human immunodeficiency virus.

1 A full physical examination will include at a minimum, assessments of the skin, cardiovascular (CV), respiratory, gastrointestinal (GI), and neurological systems.

Time and Events Table

Procedure	Period 1				Period 2							Follow-up			Notes
	Day –1	Day 1-5	Day 6-13	Day 14	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	Day 10	
Admit to clinic	X														
Discharge from clinic														X	
Brief physical examination	X												X		A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
Vital sign measurements	X	X	D7		X			X			X		X	X	
Single 12-lead ECG	X	D1			X			X			X		X		All ECGs in Period 1 and 2 will be pre-dose, post-dose at 2 hours, and post-dose 4 hours. The predose ECGs on Day 1 of both Period 1 and Period 2 will be taken in triplicate.
Drug, alcohol, and cotinine screen	X														See Appendix 2 for specific tests to be performed.
Laboratory assessments (hematology, chemistry, urinalysis)	X		D7	X			X				X		X		See Appendix 2 for specific tests to be performed.
Pregnancy test	X												X		
Columbia-Suicide Severity Rating Scale					X						X				

Procedure	Period 1				Period 2							Follow-up			Notes
	Day –1	Day 1-5	Day 6-13	Day 14	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	Day 10	
Genetic sample (Optional)	X														
Study intervention: TAF/FTC 25/200 mg		X	X	X	X	X	X	X	X	X	X				
Study intervention: GSK3640254 200 mg					X	X	X	X	X	X	X				
TAF, FTC, and TFV serial PK sampling				X	X						X	X			Blood collection for PK analysis of TAF, FTC, and TFV will be collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose (Period 1, Day 14 and Period 2, Day 7).
TAF, FTC, and TFV trough PK sampling		D2-5	X	X	X	X	X	X	X	X	X				Blood collection for TAF, FTC, and TFV trough PK samples will be collected on Period 1, Days 2 through 14 and Period 2, Days 1 through 7.
GSK3640254 serial PK sampling											X	X			Blood collection for PK analysis of GSK3640254 will be collected at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, and 24 hours postdose (Period 2, Day 7).

Procedure	Period 1				Period 2							Follow-up			Notes
	Day –1	Day 1-5	Day 6-13	Day 14	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	Day 10	
GSK3640254 trough PK sampling						X	X	X	X	X	X				Blood collection for GSK3640254 trough PK samples will be collected on Period 2, Days 2 through 7.
AE review		←==========→													
SAE review	←==========→														
Concomitant medication review	←==========→														

AE = adverse event; D = Day; ECG = electrocardiogram; FTC = emtricitabine; PK = pharmacokinetic; SAE = serious adverse event; TAF = tenofovir alafenamide; TFV = tenofovir; W = washout.

1 Evaluations scheduled for Period 2, Day 9 will also be performed for participants who discontinue early.

- The timing and number of planned study assessments, including safety, PK, or other assessments 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.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging PK data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the competent authorities (CA) and the ethics committee (EC) before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is an open-label, single-sequence, one-way drug interaction study to investigate the effect of GSK3640254 on the pharmacokinetics of tenofovir alafenamide/emtricitabine (TAF/FTC). Treatment of human immunodeficiency virus (HIV) infection frequently involves combination therapy. It is important to understand any interactions and resulting changes in exposure (if any) when HIV medications are given in combination. Data from this study will contribute to dosing recommendations when GSK3640254 and TAF/FTC are given in combination.

2.2. Background

GSK3640254 is an HIV maturation inhibitor (MI) which is improved over prior developmental MIs in the following ways: (1) it exhibits significantly improved pan-genotypic coverage and potency against polymorphic variants; (2) *in vitro* data suggest that GSK3640254 exhibits a higher barrier to emergence of resistant viruses (except for A364V); (3) GSK3640254 has improved potency *in vitro* toward all HIV-1 subtypes; (4) it has potential for improved gastrointestinal (GI) tolerability; and (5) it has a projected lower once-daily human dose. Summaries of the pre-clinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GSK Document Number 2018N379610_00].

2.2.1. Background and Key Safety Data with a Prior Maturation Inhibitor

Bristol-Myers Squibb (BMS), and later ViiV Healthcare (VH), developed a structurally similar HIV-1 MI (BMS-955176/GSK3532795), which was studied through Phase 2b studies in both treatment-naïve (AI468038/205891) and experienced (AI468048/205892) HIV-1 infected adults. In study AI468038/205891, a greater number of participants who received GSK3532795 experienced GI intolerability (most frequently Grade 1 to 2 diarrhea and abdominal pain). A detailed examination of all GI adverse events (AEs) (regardless of grade/relationship) revealed a relationship with dose [GSK Document Number 2016N302783_00]. Ultimately, the rate of GI intolerability in the GSK3532795 dose groups in the Phase 2b study 205891 led in part to VH's decision to end all trials and not progress to Phase 3 studies. Gastrointestinal AEs were also previously observed in healthy participants in Phase 1 studies with varying doses, durations, and formulations of GSK3532795. In both studies, the most common GI AEs were abdominal pain and diarrhea.

Aside from mild to moderate GI intolerability, 2 serious AEs (SAEs) occurred in the Phase I thorough QT study AI468044/206220 [BMS Document 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 AEs in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia, abnormal dreams).

2.2.2. Preliminary Safety and Pharmacokinetic Data in Study 207187

The primary objective of the first time in human (FTIH) clinical trial (207187) was to investigate the safety and tolerability of GSK3640254 following single and repeated daily administration. A total of 78 healthy men were ultimately randomized: 20 in the single-ascending dose (SAD, doses ranging from 1 to 700 mg) and 58 in the multiple-ascending dose (MAD, 50 to 320 mg QD for 14 days). A comprehensive summary of results is described in the CIB [GSK Document Number 2018N379610_00] and the Study Synopsis [GSK Document Number 2018N375461_00]. A concise summary of the data is presented below.

No deaths or SAEs were reported. There were 4 AEs leading to discontinuation. Only 1 of these AEs was related to study medication. A subject who received GSK3640254 200 mg QD developed a maculopapular rash after 8 days of study medication. The rash lasted for 6 days and there were no laboratory abnormalities. A dermatology consultant concluded this was a drug rash and the subject later received fexofenadine 180 mg QD/a topical steroid cream with resolution. The other 3 AEs occurred in SAD portion of the study (depression in a subject who received placebo and 2 subjects with viral infection).

There were 9 subjects with 12 AEs assessed as related to study medication by the principal investigator (11 Grade 1; 1 Grade 2). The most clinically notable was a subject who developed elevated transaminases while receiving GSK3640254 50 mg QD for 14 days. Specifically, there was a progressive rise in alanine aminotransferase (ALT) during treatment with a peak ALT of 83 IU/L on Day 16. The remaining liver chemistries were normal throughout. An ultrasound showed a subcapsular area of heterogenous echogenicity within segment 7, measuring approximately 35 × 23 × 36 mm. Follow-up magnetic resonance imaging and liver chemistries were normal. This subject also had 3 unrelated AEs during the course of an isolated increased ALT: musculoskeletal stiffness, contact dermatitis, and headache. All other related AEs are described in the CIB) [GSK Document Number 2018N379610_00] and the Study Synopsis [GSK Document Number 2018N375461_00].

In the SAD portion of the study, 17 subjects experienced 60 individual AEs (58 Grade 1; 2 Grade 2). The 2 Grade 2 AEs were headache and depression (both unrelated). The most frequent AEs were headache (6 subjects), contact dermatitis primarily due to electrocardiogram (ECG) electrodes (5 subjects), and diarrhea (4 subjects). There was no dose/AE relationship.

In the MAD portion of the study, 43 subjects experienced 126 individual AEs (123 Grade 1; 3 Grade 2). The 3 Grade 2 AEs were headache (1 related and 1 unrelated) and back pain (unrelated). The most frequent AEs were headache (15 subjects), contact dermatitis (8 subjects), dizziness (7 subjects), contusion (6 subjects), fatigue (6 subjects), and back pain (4 subjects).

There were no clinically significant abnormal fluctuations or trends in vital signs in the SAD or MAD cohorts. There were no abnormal clinically significant arrhythmias or QT

prolongations (values >500 msec or increases >60 msec from Baseline) observed for any participant in the SAD or MAD. There were no laboratory abnormality trends across doses that were clinically significant or associated with any symptoms.

Preliminary GSK3640254 PK parameters derived based on nominal sampling times following single doses of 1 to 700 mg administered after a moderate calorie and fat breakfast showed GSK3640254 was slowly absorbed with a median time of maximum observed concentration (Tmax) observed between 3 to 4.5 hours after dosing with a moderate fat breakfast and slowly eliminated with a mean half-life ranging from 22 to 26 hours. In general, exposure (maximum observed concentration [Cmax] and area under the plasma concentration-time curve [AUC]) increased in a close-to-dose-proportional manner from 1 to 400 mg with no further increase in exposure at 700 mg.

Repeat dose preliminary PK parameters following administration of GSK3640254 50 to 320 mg QD for 14 days were determined on Day 1 and Day 14 and showed a median Tmax ranging between 3.8 to 4.3 hours. The mean half-life ranged from approximately 22 to 29 hours. Overall, there was a trend of a slightly less than dose-proportional increase in Cmax and AUC from time 0 to 24 hours after dosing (AUC[0-24]) from 50 to 320 mg. The exposure on Day 14 was, on average, 1.9- to 2.3-fold higher than that of Day 1 for Cmax and 2.2- to 2.6-fold higher than Day 1 for AUC(0-24). Detailed summary statistics are available in the Study Synopsis [GSK Document Number 2018N375461_00].

2.2.3. Preliminary Safety and Pharmacokinetic Data in Study 208131

The FTIH Study 207187 used a bis-hydrochloride salt capsule formulation of GSK3640254, which is not suitable for long term clinical development.

Study 208131 was a single-center, open-label, 2-period, 2-sequence crossover design, conducted in 14 healthy subjects in the United Kingdom. This study was designed to assess the relative bioavailability of the formulation planned for Phase 2a (mesylate salt in a capsule) to the FTIH formulation (bis-hydrochloride salt in a capsule) administered following a moderate calorie and fat meal. All subjects completed dosing and the blinded preliminary safety data showed a total of 11 AEs (all Grade 1). Two AEs of headache were related to study drug. The most common AE was headache (3 instances). There were 3 GI AEs (abdominal pain, bleeding gums, and flatulence). There were no cardiac or psychiatric AEs. There were no clinically significant changes in vital signs, ECG parameters, or safety laboratory parameters.

Preliminary PK results from Study 208131 showed that in the presence of a moderate fat meal, the relative bioavailability of GSK3640254 following 200 mg GSK3640254 mesylate salt administration relative to 200 mg GSK3640254 bis-hydrochloride salt administration was 110% and 116% based AUC from time zero extrapolated to infinity (AUC[0-∞]) and Cmax, respectively.

2.2.4. Tenofovir Alafenamide/Emtricitabine

Descovy (tenofovir alafenamide/emtricitabine) was first approved in the United States (US) in 2015 [DESCOVY US Prescribing Information, 2017]. Tenofovir

alafenamide/emtricitabine are both HIV nucleoside analog reverse transcriptase inhibitors. Tenofovir alafenamide and emtricitabine are rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 3 hours after dose.

Tenofovir alafenamide has a 0.51-hour median plasma half-life with a mean plasma Cmax and AUC from time 0 to the end of the dosing interval at steady state (AUC[0-τ]) of 0.16 µg/mL and 0.21 µg*h/mL, respectively, after repeat dosing under fed conditions. The pharmacologically active metabolite of the TAF prodrug is tenofovir (TFV), which has a mean plasma Cmax and AUC(0-τ) of 0.02 µg/mL and 0.29 µg*h/mL, respectively, after repeat dosing under fed conditions. Emtricitabine has a 10-hour median plasma half-life with a mean plasma Cmax and AUC(0-τ) of 2.1 µg/mL and 11.7 µg*h/mL, respectively, after repeat dosing under fed conditions. Both FTC and TFV are subsequently phosphorylated intracellularly, resulting in very long (approximately 2 to 6 days) intracellular half-lives. In addition, TAF/FTC lacks many of the associated drug interactions, specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants, and other medications commonly taken by HIV-positive patients. For more details, please reference the current Descovy label [DESCOVY US Prescribing Information, 2017].

2.3. Benefit/Risk Assessment

Based upon preclinical and clinical studies, the major risks for GSK3640254 are GI intolerability (e.g., abdominal pain and diarrhea), prolongation of the corrected QT interval (QTc), and neuropsychiatric safety. Reproduction of preclinical GI toxicity findings (e.g., single-cell parietal cell necrosis) would be unlikely during the limited dosing of GSK3640254 in this study. One preclinical study showed 1 dog with an increased QTc interval when given a single dose of GSK3640254, although preliminary results from Study 207187 did not demonstrate any abnormal clinically significant arrhythmias or QTc prolongations (values >500 msec or increases >60 msec from Baseline). Finally, the protocol will exclude potential participants with any pre-existing significant psychiatric condition or positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS assessment will also be administered by a clinician (or qualified designee) during the on-treatment portion of the study.

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, and neuropsychiatric safety), this clinical study will include healthy adults who will receive clinical, ECG, and laboratory evaluations during their participation.

Tenofovir alafenamide/emtricitabine was approved in the US in 2015. The risks are outlined in the USPI [DESCOVY US Prescribing Information, 2017].

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK3640254 may be found in the CIB [GSK Document Number 2018N379610_00].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Preclinically, 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 (cDNA) 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 4 weeks. In the FTIH Study 208187, no participants exhibited QTc change from baseline >60 msec or QTc >500 msec.	**Screening**: Protocol exclusion criteria based on screening ECG parameters and cardiac medical history. **On-Treatment**: Participants will have ECG monitoring (at a clinically reasonable frequency) during the course of the study (see SoA, Section 1.3) with QTc stopping criteria (see Section 7.1.2).
Gastrointestinal (GI) intolerability and toxicity	Clinical signs indicative of GI intolerability (sporadic vomiting and abnormal feces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells were present in preclinical species. These findings were reversible. Finally, GI intolerability (predominately abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was evaluated through Phase 2b dosing.	**Screening:** Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms. **On-Treatment:** Participants will undergo continuous evaluation for AEs during their participation in the study; there will be individual clinical stopping criteria based upon intensity of treatment-emergent AEs. A GI toxicity evaluation and monitoring plan will be available to guide investigators should GI AEs emerge (See Section 8.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Neurologic/psychiatric safety	Two psychiatric serious adverse events in previous maturation inhibitor GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) were seen at supratherapeutic doses in healthy subjects in the thorough QT (TQT) study. From a neurologic and psychiatric AE summary and pharmacokinetic/pharmacodynamic analysis for GSK3532795 across all studies mild Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and Phase 2b studies). No exposure-response relationship was seen for select neurologic and psychiatric AEs (based on TQT and Phase 2b studies). Central nervous system penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration.	**Screening**: Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment) for participants. Participants will have a clinician (or qualified designee) administered Columbia-Suicide Severity Rating Scale (C-SSRS) and will be included given no positive (abnormal) response. **On-Treatment:** Participants will undergo physical examinations and laboratory testing. In addition, participants will undergo continuous evaluation for AEs during their participation in the study; there are individual clinical stopping criteria based upon incidence and intensity of treatment-emergent AEs. Participants will be housed throughout study conduct to ensure rapid diagnosis and management of any potential event. The C-SSRS will be administered during and after the treatment phase of the study. In the event of a positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management. Guidance for the investigator on the management of emergent psychiatric symptoms will be available (see Section 8.2.5). Finally, there are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 7.1.4).

2.3.2. Benefit Assessment

This is a study in healthy participants; no medical benefits will be derived by volunteers' participation.

2.3.3. Overall Benefit: Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the clinical data gathered from Studies 207187 and 208131, and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable. Descovy (tenofovir alafenamide/emtricitabine) was first approved in the US in 2015. The risks are outlined in the USPI [DESCOVY US Prescribing Information, 2017]. The potential risks to participants receiving TAF/FTC are low, evaluable, and manageable.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To assess the effect of GSK3640254 on the PK of TAF, FTC, and the active metabolite of TAF prodrug, TFV under fed conditions in healthy participants	• AUC(0-τ) and Cmax for TAF • AUC(0-τ), Cmax, and Cτ for FTC and TFV
Secondary	
• To assess the safety and tolerability of TAF/FTC administered alone and when coadministered with GSK3640254 in healthy participants	• Safety and tolerability parameters for AEs/SAEs, observed and change from baseline clinical laboratory assessments, ECGs, and vital sign measurements
• To characterize the steady-state PK of GSK3640254 in the presence of TAF/FTC in healthy participants	• AUC(0-τ), Cmax, Cτ, and Tmax for GSK3640254
• To characterize the steady-state PK of TAF, FTC, and TFV alone and in combination with GSK3640254 in healthy participants	• Tmax for TAF, FTC, and TFV

AE = adverse event; AUC (0-τ) = area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state; Cmax = maximum observed concentration; Cτ = Plasma concentration at the end of the dosing interval; ECG = electrocardiogram; FTC = emtricitabine; PK = pharmacokinetics; SAE = serious adverse event; TAF = tenofovir alafenamide; TFV = tenofovir; Tmax = time of maximum observed concentration.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, fixed-sequence 2-period, one-way drug interaction study designed to assess the PK, safety, and tolerability of GSK3640254 and TAF/FTC when administered alone and in combination in healthy participants.

The study will consist of a screening period and 2 sequential treatment periods. Participants will be screened within 28 days before the first dose of study intervention. The treatments will be as follows:

- Treatment A: TAF/FTC 25/200 mg QD on Days 1 through 14 (Period 1)
- Treatment B: TAF/FTC 25/200 mg QD coadministered with GSK3640254 200 mg QD on Days 1 through 7 (Period 2)

There is no washout between the last dose of study intervention (Treatment A) in Period 1 and initiation of study intervention (Treatment B) in Period 2. The participants will fast overnight for at least 8 hours prior to dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Pharmacokinetic blood samples for analysis of TAF, FTC, and TFV will be collected before dosing (0 hour) on Days 2 through 14 (Period 1) and Days 1 through 7 (Period 2) and up to 24 hours after TAF/FTC dosing on Period 1, Day 14 and Period 2, Day 7. Pharmacokinetic blood samples for analysis of GSK3640254 will be collected before dosing (0 hour) on Days 2 through 7 (Period 2) and up to 24 hours after GSK3640254 dosing on Day 7.

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings.

Study assessments will be performed as indicated in the Schedule of Activities (SoA) (Section 1.3). Participants will be confined to the clinic from Day –1 until discharge on Period 2, Day 10.

4.2. Scientific Rationale for Study Design

This is an open-label, single-sequence, one-way drug interaction study to investigate the PK interactions between GSK3640254 and TAF/FTC. Treatment of HIV infection frequently involves combination therapy. It is important to understand any interactions and resulting changes in exposure (if any) when HIV medications are given in combination, and any subsequent dosing modifications recommended.

The inhibitory potential (direct and metabolism-dependent inhibition) of GSK3640254 towards 7 major human hepatic cytochrome P450 (CYP) enzymes was evaluated in human liver microsomes (CIB) [GSK Document Number 2018N379610_00].

GSK3640254 demonstrated minimal direct inhibition of all 7 CYP isoforms tested (half maximal inhibitory concentration [IC50] values >13.3 μM). At the maximum projected clinical dose of 200 mg, there is a low risk for clinically meaningful CYP-mediated drug-drug interactions (DDIs) with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

GSK3640254 did not demonstrate human pregnane X receptor or vitamin D receptor mediated transactivation of CYP3A. Therefore, it is unlikely that GSK3640254 would induce CYP3A, or other pregnane X receptor and vitamin D receptor regulated enzymes/transporters in humans. In addition, GSK3640254 was tested in a panel of CYP induction assays using inducible cryopreserved human primary hepatocytes and showed no induction (EC50 >5 μM) of CYP3A4, CYP2B6, and CYP1A2.

GSK3640254 is an inhibitor of organic anion-transporting polypeptide (OATP)1B3 and multi-drug resistance protein (MRP)2 in vitro and has a potential of generating DDIs with substrates of these transporters at the projected human systemic exposures. The IC50 values of GSK3640254 against OATP1B3 and MRP2 were 0.55 and 2.2 μM, respectively. In addition, GSK3640254 was an inhibitor of uridine diphosphate glucuronosyltransferase (UGT)1A1 in vitro (IC50 = 3.9 μM) and clinical DDIs via this mechanism could be possible although literature reports have not revealed clinical DDIs with greater than 2-fold change in exposure, with a few exceptions, due to UGT1A1 inhibition [Lin, 2002, Williams, 2004]. Clinically meaningful DDI risk due to UGT1A1 inhibition by GSK3640254 is likely minimal. Tenofovir alafenamide (a substrate of p-glycoprotein, breast cancer-resistant protein, OATP1B1, and OATP1B3) and FTC are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. GSK3640254 is an inhibitor of OATP1B3; however, there is a low risk of meaningful DDI as TAF elimination primarily occurs in urine. This study will aid in understanding these interactions and resulting changes in exposure (if any) when given in combination.

This study is designed in accordance with the US Food and Drug Administration Guidance for Industry, Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications [DHHS, 2017] to assess the PK, safety, and tolerability of GSK3640254 and TAF/FTC when administered alone and in combination.

4.3. Justification for Dose

The doses of 200 mg GSK3640254 and 25/200 mg TAF/FTC were selected for this study. The maximum projected clinical dose of GSK3640254 is 200 mg QD. The apparent terminal phase half-life (t1/2) of GSK3640254 was approximately 22 hours in the MAD portion of Study 207187 at the 200-mg dose, and predicted time to steady state is approximately 5 days. Tenofovir alafenamide/emtricitabine 25/200 mg QD was selected for this study because it is the currently recommended dose for HIV-infected patients. The t1/2 of TAF is approximately 0.5 hours and the t1/2 of FTC is approximately 10 hours.

Dosing of GSK3640254 QD from Period 2, Days 1 to 7 should be sufficient to bring plasma concentrations to steady state. There is no subsequent need for a washout of

GSK3640254 since the primary remaining evaluation is for coadministered TAF/FTC and GSK3640254 at steady state.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the final date on which data were or are expected to be collected.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for 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.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG).

Weight

3. Body weight ≥50.0 kg (110 lbs) for men and ≥45.0 kg (99 lbs) for women and body mass index (BMI) within the range 18.5 to 31.0 kg/m^2 (inclusive).

Sex

4. Male or female

   a. Female participants:

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and not a woman of childbearing potential (WOCBP) as defined in Appendix 3.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 4 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical History

1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
2. A pre-existing condition interfering with normal GI anatomy or motility (e.g., gastroesophageal reflux disease, gastric ulcers, gastritis), hepatic and/or renal function, that could interfere with the absorption, metabolism, and/or excretion of the study drugs or render the subject unable to take oral study intervention.
3. Any history of significant underlying psychiatric disorder including, but not limited to, schizophrenia, bipolar disorder with or without psychotic symptoms, other psychotic disorders, or schizotypal (personality) disorder.
4. 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. 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.
5. Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the investigator (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.
6. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
7. History of any kidney disease or current or chronic history of impaired renal function as indicated by an estimated creatinine clearance <80 mL/min.

   Creatinine clearance (CrCL) is estimated by either of the following methods:

   a. the Modification of Diet in Renal Disease (MDRD) equation:

      $eGFR(mL/min/1.73\ m^2) = 175 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times 0.742$ [if female] x 1.212 [if African American]

      GFR is expressed in mL/min/1.73 m^2, S_{Cr} is serum creatinine expressed in mg/dL, and age is expressed in years.

   b. the Cockcroft-Gault equation:

      $CrCL(mL/min) = \{((140 - age) \times weight)/(72 \times S_{Cr})\} \times 0.85$ (if female)

      CrCL is expressed in mL/min, age is expressed in years, weight is expressed in kg, and S_{Cr} is serum creatinine expressed in mg/dL

Laboratory Assessments

8. Presence of Hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to starting study intervention.
9. Positive Hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention AND positive on reflex to Hepatitis C RNA.
10. Positive HIV-1 and -2 antigen/antibody immunoassay at Screening.
11. ALT >1.5 × upper limit of normal (ULN). A single repeat of ALT is allowed within a single screening period to determine eligibility.
12. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
13. Any acute laboratory abnormality at Screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
14. Any Grade 2 to 4 laboratory abnormality at Screening, with the exception of creatine phosphokinase (CPK) and lipid abnormalities (e.g., total cholesterol, triglycerides, etc), and ALT (described above), will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.
15. A positive test result for drugs of abuse (including marijuana), alcohol, or cotinine (indicating active current smoking) at Screening or before the first dose of study intervention.

Prior/Concomitant Therapy

16. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and for the duration of the study.
17. Treatment with any vaccine within 30 days prior to receiving study intervention.
18. Unwillingness to abstain from excessive consumption of any food or drink containing grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study.

Prior/Concurrent Clinical Study Experience

19. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the study intervention (whichever is longer).
20. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.

Diagnostic Assessments

21. Any positive (abnormal) response confirmed by the investigator on a screening clinician- or qualified designee-administered C-SSRS.
22. Any significant arrhythmia or ECG finding (e.g., prior myocardial infarction, sinoatrial pauses, bundle branch block, or conduction abnormality) which, in the opinion of the investigator or VH/GSK Medical Monitor, will interfere with the safety for the individual participant.
23. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<45 or >100 bpm	<50 or >100 bpm
PR Interval	<120 or >200 msec	
QRS duration	<70 or >110 msec	
QTcF interval	>450 msec	>470 msec

Note: A heart rate from 100 to 110 bpm can be rechecked by ECG or vital signs within 30 minutes to verify eligibility.

Other Exclusions

24. History of regular alcohol consumption within 6 months of the study defined as: an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.
25. Regular use of tobacco- or nicotine-containing products within 3 months prior to Screening.
26. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from excessive consumption of red wine, grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study. Excessive consumption is defined as more than one glass of wine or juice or one fruit per day, in combination.
- Unless otherwise indicated, all doses of GSK3640254 and TAF/FTC in this study will be administered in the fed state. The participants will fast overnight for at least 8 hours prior to dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours post-dose on serial PK sampling days (Period 1, Day 14 and Period 2, Day 7).

The moderate fat meal will contain about 600 calories with approximately 30% of them coming from fat.

- No water is allowed from 2 hours prior to dosing until 2 hours after dosing except for the glass of water needed to administer the study intervention (e.g., 240 mL). Water is allowed ad libitum at all other times.
- A standard lunch will be provided 4 hours after dosing. A standard dinner will be served approximately 10 hours after dosing. The food content of meals must be identical on serial PK sampling days.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 48 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco and nicotine-containing products will not be allowed from 3 months prior to Screening until after the final visit.
- Participants must have a negative drug test at Screening and Day –1, and must abstain from recreational drug use from Screening until after the final visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

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

Intervention Name	GSK3640254	Descovy (tenofovir alafenamide/emtricitabine)
Type	drug	drug
Dose Formulation	capsule	tablet
Unit Dose Strength(s)	100 mg	25/200 mg
Dosage Level(s)	200 mg once daily	25/200 mg once daily
Route of Administration	oral	oral
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Purchased by the Investigator
Packaging and Labeling	Provided in high-density polyethylene (HDPE) bottles. Each bottle will be labeled as required per country requirement.	Provided in HDPE bottles. Each bottle will be labeled as required 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 Study Reference Manual (SRM).
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet/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 VH/GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. All participants will receive the same treatment.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Acetaminophen/paracetamol at doses of ≤2 grams/day are permitted for use any time during the study and their use documented in the CRF.

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from VH/GSK, or with GSK3640254 or TAF/FTC, after the completion of the study because only healthy volunteers are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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 remain in the study to be evaluated for safety. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration premarketing clinical liver safety guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf).

Discontinuation of study intervention for abnormal liver tests is required when a participant has an ALT ≥3 × ULN or if the investigator believes study intervention discontinuation is in the best interest of the participant.

Details of liver safety follow-up procedures are described in Appendix 5.

7.1.1.1. 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.

7.1.2. QTc Stopping Criteria

The *same* Fridericia QT correction formula (QTcF) *must* be used for *each individual 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 (e.g., 5-10 minute) recording period from the Day 1 pre-dose ECG.
- A randomized participant that develops an on-treatment QTcF >500 msec or an increase from baseline QTcF >60 msec should have two repeat unscheduled ECG's within 10 minutes. Using these triplicate ECGs, if the average QTcF >500 msec or an increase from baseline QTcF >60 msec, the participant will be withdrawn from the study. Finally, this participant should have repeated unscheduled ECGs until their QTcF 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.

7.1.3. Columbia-Suicide Severity Rating Scale Criteria

Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered C-SSRS during the on-treatment phase of the study will be cause for discontinuation of study intervention.

Refer to 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.

7.1.4. Individual Participant Laboratory Abnormality and Adverse Event Stopping Criteria

Investigators should make every effort to have a discussion with the medical monitor before the next dose to help assess if the study intervention should be stopped.

- Any clinically significant AE deemed to require discontinuation of study intervention
- Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement
- Any allergic or hypersensitivity reactions to either or both drugs
- Any Grade 3 or higher psychiatric AE
- New onset suicidal ideation
- Any Grade 3 or higher AE related to study intervention
- Any Grade 4 AE or laboratory abnormalities (with the exception of an asymptomatic Grade 4 cholesterol, triglyceride, or CPK increase)

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, compliance, or administrative reasons. This is expected to be uncommon.
- A subject who is withdrawn from the study for any reason related to safety (listed in Section 7.1.4 or otherwise) will be continued to be followed to assess the outcome of the safety event that triggered discontinuation of study drug.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 4.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Not applicable.

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 full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-recumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 blood pressure and pulse measurements (3 consecutive blood pressure and pulse readings will be recorded at intervals of at least 1 minute). Each measurement will be recorded in the case report form (CRF).

8.2.3. Electrocardiograms

- On Period 1, Day 1 and Period 2, Day 1, triplicate ECGs will be taken prior to dosing. The ECGs should be recorded over a brief (e.g., 5 to 10 minutes) recording period. Each measurement will be recorded in the CRF.
- Single 12-lead ECG will be obtained at other time points as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- Twelve-lead ECGs will be performed with the participant in a supine or semi-supine position after a rest of at least 10 minutes.
- At each time point at which triplicate ECGs 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 over a brief (e.g., 5 to 10 minutes) recording period.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or Baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Suicidal Risk Monitoring and Management of Emergent Psychiatric Symptoms

GSK3640254 is not a central nervous system active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with previous MI GSK3532795, all participants will undergo screening using the C-SSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator will exclude them from participating. A repeat assessment will be done at the end of the treatment phase of the study. In case of positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management.

As described in Section 7.1.4, new onset suicidal ideation at any time will result in immediate discontinuation from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management.

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) and all subsequent questioning in relation to the last assessment.

Emergent non-suicidal Psychiatric AE Evaluation and Management:

- 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 investigator. Any pharmacotherapy should be discussed with the medical monitor.

- Any Grade 3 or 4 psychiatric AE: As described in Section 7.1.4, a Grade 3 or 4 psychiatric AE will result in discontinuation from the trial and emergency psychiatric evaluation (including potential hospitalization and pharmacotherapy as indicated).

8.2.6. Gastrointestinal Toxicity Evaluation and Monitoring Plan

Preclinical toxicology studies in rats and dogs have suggested a potential for GI-related toxicity with GSK3640254. This section provides general guidance to the investigator on the evaluation and management of primarily upper GI symptoms (Table 1). The investigator may contact the VH/GSK Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the study.

Table 1 Gastrointestinal Toxicity Evaluation and Management

HISTORY	**For symptoms of all grades, a thorough history 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 study.**
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]. Medications can cause nausea and vomiting acutely.
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.
Other Clinical Syndromes	Additional diagnostic criteria for other GI disorders potentially encountered in the clinical study are available elsewhere [Rome Foundation, 2018].
PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history [Hasler, 2012]. 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. Consultation (e.g., gastroenterologist) is recommended as clinically indicated.**
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.
Grade 2 symptoms	Diagnostic testing may include but is not limited to the following (as clinically indicated): • Serum chemistries and assessment of hemoglobin if not recently performed • Testing for *Helicobacter pylori* • Polymerase chain reaction for viruses (e.g., cytomegalovirus) For participants who are infected with *H. pylori*, discontinuation from the study is necessary. Management should be targeted at addressing the underlying pathology.
Grade 3 symptoms [1]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • Computed tomography scan to identify GI inflammation • Upper endoscopy with biopsy as indicated (e.g., mucosal injury or the presence of red flags) Management should be targeted at addressing the underlying pathology.
Grade 4 symptoms [1]	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 Initial management can include correction of hemodynamic and electrolyte abnormalities as clinically indicated. After stabilization, management should be targeted at addressing the underlying pathology.

GI = gastrointestinal.

1 A Grade 4 or related Grade 3 AE: The Investigator will discontinue the participant from the study and perform an evaluation/management plan incorporating elements above.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 6. As described in Appendix 6, intensity of AEs (and laboratory abnormalities) will be graded using the most recent version of the Division of AIDS (DAIDS) grading table at the time of the last participant last visit. While the study population will consist of HIV-1 seronegative healthy volunteers, the DAIDS criteria will be used in later clinical studies (Phase 2a and beyond); additionally, the DAIDS criteria have a more conservative grading scale relative to other scales (e.g., CTCAE v 4.0). Thus, participant safety evaluation and monitoring will be more conservative.

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 to discontinue the study (see Section 7).

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

- All SAEs will be collected from the signing of the ICF until the end of the study at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the end of the study 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 CRF, not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs 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

- The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.
- Care will be taken not to introduce bias when detecting an 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 Appendix 6.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an 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, IRB/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 SAEs) from the sponsor will review and then file it along with the CIB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and through the end of pregnancy (termination or delivery).
- If a pregnancy is reported, the investigator should inform VH/GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, any dose of GSK3640254 or TAF/FTC greater than the planned dose within a 24-hour time period (±2 hours) will be considered an overdose.

VH/GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat 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 GSK3640254 or TAF/FTC can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis immediately and through 7 days after 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 CRF.

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

8.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the SoA (Section 1.3).
- Separate whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of TAF, FTC, and TFV as specified in the SoA (Section 1.3).
- A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3640254 and TAF, FTC, and TFV. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of GSK3640254 and TAF, FTC, and TFV plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK3640254 and TAF, FTC, and TFV, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

8.6. Pharmacodynamics

Pharmacodynamic endpoints are not evaluated in this study.

8.7. Genetics

A 10-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the 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 Appendix 7 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal research hypothesis that will be statistically tested in this study. Coadministration of GSK3640254 and TAF and FTC may increase the exposure of TAF, FTC, and the metabolite TFV, and coadministration of GSK3640254 with TAF and FTC are expected to have no significant impact on the exposure of GSK3640254.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

Based on the results from a previous PK study for TAF and FTC (GS-US-120-0118) the intra-subject coefficient of variation (CVw) was <20% for AUC(0-τ) and Cmax. Therefore, it is decided that 20% would be a conservative estimate on which the sample size calculation is based. Since it is expected that coadministration of GSK3640254 and TAF/FTC may increase the exposure of TAF, FTC, and the metabolite TFV, a range for point estimate (PE) for a ratio of 1.0, 1.1, and 1.2 were explored.

Based on the results from preliminary PK studies for GSK3640254 (GSK Study 207187 and 208131) the CVw ranged from 17% to 38% and 13% to 31%, respectively, for AUC (0-τ) and Cmax. Therefore, it is decided that 38% would be a conservative estimate on which the sample size calculation is based. Since it is expected that coadministration of GSK3640254 with TAF/FTC is expected to have no significant impact on the exposure of GSK3640254 a range for PE for a ratio of 0.9, 1.0, and 1.1 were explored.

For TAF/FTC, with a sample size of 12 evaluable subjects, it is estimated that the precision (i.e., half-width of the 90% confidence interval [CI] on the log and ratio scale), and CI on the original scale for each PE will be as follows:

Drug	CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
TAF/FTC	20	0.145	0.156	1.0	(0.865, 1.156)
				1.1	(0.952, 1.272)
				1.2	(1.038, 1.387)

For GSK3640254, with a sample size of 12 evaluable subjects, it is estimated that the precision (i.e., half-width of the 90% CI on the log and ratio scale), and CI on the original scale for each PE will be as follows:

Drug	CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
GSK3640254	38	0.269	0.309	0.9	(0.688, 1.178)
				1.0	(0.764, 1.309)
				1.1	(0.841, 1.440)

9.2.2. Sample Size Sensitivity

For a sensitivity analysis, assuming a range of within-subject variability, a sample size of 12 evaluable subjects, it is estimated that the precision (i.e., half-width of the 90% CI on the log and ratio scale), and CI on the original scale for each PE will be as follows:

Drug	CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
TAF/FTC or GSK3640254	10	0.073	0.076	0.9	(0.837, 0.968)
				1.0	(0.930, 1.076)
				1.1	(1.023, 1.183)
				1.2	(1.116, 1.291)
	20	0.145	0.156	0.9	(0.779, 1.040)
				1.0	(0.865, 1.156)
				1.1	(0.952, 1.272)
				1.2	(1.038, 1.387)
	30	0.215	0.240	0.9	(0.726, 1.116)
				1.0	(0.807, 1.240)
				1.1	(0.887, 1.364)
				1.2	(0.968, 1.488)
	40	0.283	0.327	0.9	(0.678, 1.194)
				1.0	(0.754, 1.327)
				1.1	(0.829, 1.460)
				1.2	(0.904, 1.593)

Approximately 16 participants will be treated to ensure that 12 evaluable participants complete the study.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Safety	All participants who receive at least 1 dose of study medication. This population will be used for all demographic and safety summaries.
Pharmacokinetic Concentration	The PK Concentration Population will include all participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the concentration listing.
Pharmacokinetic Parameter	The PK Parameter Population will include all participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listing, plotting of the concentration-time data and PK parameter summary.

9.4. Statistical Analyses

9.4.1. Pharmacokinetic Analyses

Plasma GSK3640254 and TAF, FTC, and TFV concentration-time data will be analyzed by PPD, under the oversight of Clinical Pharmacology Modeling & Simulation department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 6.4 or higher. Statistical analysis will be performed by PPD, under the oversight of Clinical Statistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

Endpoint	Statistical Analysis Methods

Primary	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of TAF, FTC, and TFV will be subjected to PK analyses using noncompartmental methods.
	• Based on the individual concentration-time data the following primary plasma parameters will be estimated:
	  • TAF (Periods 1 and 2): AUC(0-τ) and Cmax
	  • FTC and TFV (Periods 1 and 2): AUC(0-τ), Cmax, and Cτ
	• Analyses will be performed to assess the effect of GSK3640254 on the PK of TAF, FTC, and TFV, as appropriate. Analyses will be performed on the natural logarithms of AUC(0-τ), Cτ, and Cmax using linear mixed-effect models with treatment as a fixed effect and subject as a random effect. Effects will be estimated, and CIs will be constructed for the following treatment comparison:
	  • Period 2 versus Period 1
	• Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.
	• Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma TAF, FTC, and TFV PK parameter values will be summarized by study day.

Secondary	• Plasma concentrations of GSK3640254 will be subjected to PK analyses using noncompartmental methods.
	• Based on the individual concentration-actual time data the following secondary plasma parameters will be estimated:
	  • TAF, FTC, and TFV (Periods 1 and 2): Tmax
	  • GSK3640254 (Period 2): AUC(0-τ), Cmax, Cτ, and Tmax (note: GSK3640254 PK parameter values in the presence of TAF/FTC from this study will be compared with GSK3640254 PK parameter values from previous studies)
	• Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 and TAF, FTC, and TFV PK parameter values will be summarized by study day.
	• Additionally, predose (trough) PK plasma concentrations (TAF, FTC, and TFV: Days 2 through 14 [Period 1] and 1 through 7 [Period 2]; GSK3640254: Days 2 through 7 [Period 2]) will be summarized using the PK Concentration Population, and used to assess achievement of steady state.

Exploratory	Will be described in the reporting and analysis plan

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

The details of the statistical analyses of safety and PK data will be provided in the reporting and analysis plan.

9.4.3. Other Analyses

Not applicable.

9.5. Interim Analyses

No interim analysis is planned.

9.5.1. Data Monitoring Committee (DMC)

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC(0-τ)	Area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state
AUC(0-24)	Area under the plasma concentration-time curve from time 0 to 24 hours after dosing
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
CA	Competent Authorities
cDNA	Complementary Deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	Confidence interval
CIB	Clinical Investigator's Brochure
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
Cτ	Plasma concentration at the end of the dosing interval
CV	Cardiovascular
CVw	Intra-subject coefficient of variation
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
EC	Ethics Committee
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
FTC	Emtricitabine
FTIH	First-time-in-human
GCP	Good Clinical Practice

GI	Gastrointestinal
GSK	GlaxoSmithKline
IC50	Half maximal inhibitory concentration
HBsAg	Hepatitis B surface antigen
HDPE	High-density Polyethylene
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
MAD	Multiple-ascending dose
µg	Micrograms
mg	Milligrams
MI	Maturation inhibitor
MRP	Multi-drug resistance protein
OATP	Organic anion-transporting polypeptide
PE	Point estimate
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	Fridericia QT correction formula
SAD	Single-ascending dose
SAE	Serious adverse event
SoA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Terminal phase half-life
TAF/FTC	Tenofovir alafenamide/emtricitabine
TFV	Tenofovir
Tmax	Time of maximum observed concentration
TQT	Thorough QT
UGT	Uridine diphosphate glucuronosyltransferase

ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
VH	ViiV Healthcare
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
DAIDS
DESCOVY

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the time points indicated in the SoA (Section 1.3).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count Red Blood Cell Count Hemoglobin Hematocrit	Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry [1]	Blood urea nitrogen	Aspartate aminotransferase	Globulin
	Creatinine Glucose (fasting) Potassium Sodium Calcium Chloride Phosphorus Carbon dioxide	Alanine aminotransferase Gamma-glutamyl transferase Total and direct bilirubin Lactate dehydrogenase Total cholesterol Triglycerides Total protein Albumin	Anion gap Alkaline phosphatase Uric acid Creatine phosphokinase Serum lipase Serum amylase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood, leukocyte esterase, or protein is abnormal)		

Laboratory Assessments	Parameters
Other Screening Tests	• Serology: HIV-1 and -2 antigen/antibody immunoassay, Hepatitis B surface antigen (HBsAg), Hepatitis C (Hep C antibody) • Alcohol, cotinine, and drug screen (to include at minimum amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Pregnancy [2]

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 Appendix 7. All events of ALT ≥3 ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

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.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - 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., müllerian agenesis, androgen insensitivity), 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.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement (>40 IU/L or mIU/mL) is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 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.

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

10.4.1. 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 International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, CIB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.4.2. 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.

10.4.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants 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 remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

10.4.4. Data Protection

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

10.4.5. 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.

10.4.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a VH/GSK site or other mutually-agreeable location.
- VH/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with VH/GSK Policy.
- VH/GSK intends to make anonymized patient-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding.

10.4.7. 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report/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.

10.4.8. 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 can be found in the SRM.

10.4.9. Study and Site Closure

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

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

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

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

10.4.10. 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.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

The procedures listed below are to be followed if a participant meets the liver chemistry stopping criteria defined in Section 7.1:

- Immediately withdraw the participant from study intervention
- Notify the VH/GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the participant's study intervention cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event CRFs. If the event also meets the criteria of an SAE (see Appendix 6), the SAE data collection tool will be completed separately with the relevant details.

Safety Follow-Up Procedures for participants with ALT ≥3 × ULN:

- Monitor participants weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase, bilirubin) resolve, stabilize, or return to within baseline values.

Safety Follow-Up Procedures for participants with ALT ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin); or ALT ≥3 × ULN and INR1 >1.5:

- This event is considered an SAE (see Appendix 6). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have participants return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor participants twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize, or return to within baseline values.

In addition, for all participants with ALT ≥3 × ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including: Hepatitis A IgM antibody, Hepatitis B surface antigen, and Hepatitis B Core Antibody (IgM), Hepatitis C RNA, Cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), Hepatitis E IgM antibody.
- Blood sample for PK analysis, obtained within 48 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the 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 included in the SRM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2 × ULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are required for participants with ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- 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]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

10.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. 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 <u>Meeting</u> 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 DDI. • 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.

Events <u>NOT</u> 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.

10.6.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- 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.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. 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.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.6.3. 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 (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to VH/GSK in lieu of completion of the GSK AE/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 VH/GSK.
- 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.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf) and assign it to 1 of the following categories:

- Mild: no or minimal interference with usual social & functional activities
- Moderate: greater than minimal interference with usual social and functional activities
- Severe: inability to perform usual social and functional activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- Life Threatening: inability to perform basic self-care functions

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

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the CIB 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 VH/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to VH/GSK.** • 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 1 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 VH/GSK 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 VH/GSK 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 VH/GSK within 24 hours of receipt of the information.

10.6.4. Reporting of SAE to VH/GSK

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

SAE Reporting to VH/GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical 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 SRM.

10.7. Appendix 7: 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 HIV MIs and HIV. Genetic research may consist of the analysis of 1 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.

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