TITLE PAGE

Protocol Title: A Randomized, Double-Blind (Sponsor-unblinded), Placebo-Controlled, Adaptive Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of GSK3640254 in HIV-1 Infected Treatment-Naïve Adults

Protocol Number: 208132 / 03

Short Title: GSK3640254 POC in Treatment-Naïve Adults

Compound Number: GSK3640254

Sponsor Name and Legal Registered Address (excluding US):
ViiV Healthcare UK Limited
980 Great West Road
Brentford Middlesex, TW8 9GS, UK

US IND Sponsor Name and Legal Registered Address:
ViiV Healthcare Company
Five Moore Drive,
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

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

This study is sponsored by ViiV Healthcare. GlaxoSmithKline (GSK) is supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information

PPD, DO, MPH
PPD
PPD USA mobile
USA fax

Regulatory Agency Identifying Number(s):

IND #: 139,838 EudraCT#: 2018-002208-15

Approval Date: 26-AUG-2019

SPONSOR SIGNATORY:

PPD

8/26/2019

Ma lade, DO, MPH Date
Vic lent, Clinical Development
ViiV Healthcare

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	26-Aug-2019
Amendment 2	10-Jan-2019
Amendment 1	28-Sep-2018
Original Protocol	15-Aug-2018

Amendment 3 26-AUG-2019

Overall Rationale for the Amendment: Data from Part 1 showed a decline in HIV-1 RNA and reasonable PK profile. There were no clinically significant trends in AEs, vital signs, ECG findings, or chemistry/haematology laboratory abnormalities across dosing arms. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on or after Day 11 (after 10 days of receiving GSK3640254 monotherapy). Additionally, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed at Day 11 as there is no known cross-resistance between maturation inhibitors and other classes of ARVs. Genotypic analysis of samples at Clinic Visit 5 (Study Day 8 or 9) revealed no treatment emergent resistance. As a result, Sponsor made two substantial changes to decrease the risk of treatment emergent resistance to participants in Part 2: 1) decrease the duration of monotherapy from 10 days to 7 days based on the interim genotypic analysis, and 2) start Investigator selected cART immediately after completion of monotherapy and the Part 2 primary endpoint (i.e., after the collection of HIV-1 RNA on Day 8).

Section # and Name	Description of Change	Brief Rationale
Synopsis, Objectives and Endpoints Synopsis, Overall Design Synopsis, 208132 Study Schematic Synopsis, Treatment Groups and Duration Section 3.1, Study Rationale Section 3.3.2, Benefit Assessment Section 3.3.3, Overall Benefit:Risk Conclusion Section 4, Objectives and Endpoints Section 5.1, Overall Design Section 5.1.1.1, Screening Phase Section 5.1.1.2, Treatment Phase and Follow-up Period, and to include the 208132 Study Schematic Section 5.5, Dose Justification Section 6.3.1, Meals and Dietary Restrictions Section 6.3.2, Alcohol, Tobacco and Marijuana Section 6.3.3, Activity Section 7.8, Treatment and Care After the End of the Study Section 8.2, Withdrawal from the Study Section 9.5, Pharmacokinetics, and to include Table 4	Changes in these sections are all related, in total or in part, to the changes made to Study Part 2 relative to Study Part 1: • reduction of the treatment period from 10 days to 7 days, • reduction of the number of study visits • reduction of the number of days of overall study participation.	To decrease the risk of treatment emergent resistance in the setting of GSK3640254 monotherapy.

Section # and Name	Description of Change	Brief Rationale
Section 9.8, Biomarkers Section 10.1.1, Sample Size Considerations Section 10.3.2.3, Pharmacokinetic Analysis		
Synopsis, Treatment Groups and Duration Section 5.1.1.2, Treatment Phase and Follow-up Period Section 7.8, Treatment and Care After the End of the Study	Provided instruction that cART should be initiated in study Part 2 immediately after treatment period ends/on Day 8	To reduce the risk to participants for treatment emergent resistance in the setting of GSK3640254 monotherapy.
Section 2.2, Part 1 and Part 2 Treatment, Post-Dosing and Follow-up Periods	Labelled the original SoA table as being specific to study Part 1. Created another SoA table specific to study Part 2 to include the 7-day treatment period duration and abbreviated follow-up period and associated assessments and procedures: • Clinic Visit 4 was modified to be conducted only on Days 5 and 6. • Clinic Visit 5 was modified to be conducted only on Day 7. • Clinic Visit 6 was modified to be conducted only on Day 8 • Clinic Visit 7 was modified to be the Final Follow-up Visit and to be conducted on Days 10, 11 or 12. • Clinic Visits 8 and 9 were removed • Days 13-24 were removed • A line item was added for the task of observing the dosing with cART on Day 8 • Footnotes used in study Part 1	To reflect the treatment duration and post-dosing period modifications for Part 2 as made in protocol text.

Section # and Name	Description of Change	Brief Rationale
	were applied, but modified to be appropriate to the needs and requirements for study Part 2	
Section 3.2.2, Preliminary Safety and PK Data in Study 207187	Provided updated information regarding the 207187 study.	More current information is now available.
Section 3.2.4, Justification for Part 2 Treatment Duration and Initiation of cART	Described the data-driven decisions made with the resistance data from study Part 1, resulting in the 2 key changes to be applied in study Part 2 – to treat for 7 days instead of 10 days, and to initiate cART immediately after the treatment period instead of at the end of the post-doing period.	To justify the 2 primary changes in this amendment.
Section 3.3, Benefit/Risk Assessment	Provided updated information relative to the risk of treatment emergent resistance in the setting of GSK3640254 monotherapy	More current information is now available.
Section 3.3.1, Risk Assessment	Cardiovascular category, Risks column: Updated with new information pertaining to the risks for Cardiovascular (QT Prolongation)	More current information is now available.
	HIV Resistance to GSK3640254 category, Risks column: Summarized the analyses of the treatment emergent resistance that was observed after 10 days of monotherapy in Part 1.	Full analyses of resistance data revealed additional risk for treatment emergent resistance.
	HIV Resistance to GSK3640254 category, Mitigation Strategy column: Summarized the actions to be taken in study Part 2 to reduce the risk to participants for treatment emergent resistance.	To provide additional mitigation corresponding to the additional risk.
Section 6.1, Inclusion Criteria	Inserted new criterion #10	The addition was made to reinforce the requirement that

Section # and Name	Description of Change	Brief Rationale
		cART must be started on Day 8.
Section 12.2, Clinical Laboratory Tests, Table 7, Protocol Required Safety Assessments	Add the caveat that glucose cannot be done in a non-fasted state on clinic days when fasting lipids are also collected.	For clarity.
Other administrative changes	Minor editorial and document formatting revisions	Minor, therefore not summarized

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Randomized, Double-Blind (Sponsor-unblinded), Placebo-Controlled, Adaptive Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of GSK3640254 in HIV-1 Infected Treatment-Naïve Adults

Short Title: GSK3640254 POC in Treatment-Naïve Adults

Rationale:

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

GSK3640254 is a next-generation HIV-1 Maturation Inhibitor (MI) which binds near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton (kDa) HIV capsid (CA) protein p24 (CA [p24]) and spacer peptide 1 (SP1). Blockage at this step results in the release of immature non-infectious virus particles.

The clinical development of GSK3640254 is progressing. Study 207187 is the First Time in Human (FTIH) study of GSK3640254 investigating the safety, tolerability, and pharmacokinetics (PK) of single and repeated escalating doses in healthy participants. Healthy participants not receiving placebo have received GSK3640254 to a maximum single dose of 700 mg and multiple doses up to 320 mg QD for 14 days. Study 207187 has shown GSK3640254 to be generally well-tolerated in healthy volunteers to date and has thus far demonstrated a PK profile suitable for progression to HIV-1 infected treatment naïve (TN) patients in this Phase 2a proof of concept (POC) 10-day, monotherapy study.

The FTIH Study 207187 uses a bis-hydrochloride salt capsule formulation of GSK3640254, which is not suitable for long term clinical development. The relative bioavailability Study 208131 assessed the relative bioavailability of a mesylate salt capsule formulation of GSK3640254 intended for use in this POC study, compared to the hydrochloride salt capsule formulation used in the FTIH study. Preliminary 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 107% and 110% based on AUC(0-∞) and maximum observed concentration (Cmax), respectively.

Data from these studies will be utilized to support future clinical development of GSK3640254.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of GSK3640254 in HIV-1 infected TN participants during 10 days of monotherapy in Part 1 and during 7 days of monotherapy in Part 2	• Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA)
Key Secondary	
• To assess the safety and tolerability of GSK3640254 when administered as monotherapy over 10 days in Part 1 and over 7 days in Part 2 in HIV-1 infected TN participants	• GSK3640254 safety and tolerability parameters: adverse events (AE); post-baseline values and changes over time of clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters.
• To characterize the pharmacokinetics of GSK3640254 dosing for 10 days in Part 1 and for 7 days in Part 2 in HIV-1 infected patients	• GSK3640254 PK parameters at the following dose administration: **Day 1**: area under the plasma concentration time curve from zero to 24 (AUC [0-24]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag) Following repeat administration: Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC [0-τ]), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), apparent terminal phase half-life (t1/2), and apparent oral clearance (CL/F), if data permit.
• To explore the relationship between GSK3640254 exposure and change in plasma HIV-1 RNA	• GSK3640254 repeat-dose PK parameters AUC(0-τ), Cmax, Cτ with maximum HIV-1 RNA change from baseline

Objectives	Endpoints
• To estimate GSK3640254 accumulation following administration of GSK3640254 for 10 days in Part 1 and for 7 days in Part 2 in HIV-1 infected patients.	• Accumulation: GSK3640254 PK accumulation ratios (R): repeat -dose AUC (0-τ), Cmax, and Cτ compared to Day 1 AUC (0-24), Cmax, C24, respectively
• To examine dose proportionality of GSK3640254 PK parameters following dosing for 10 days in Part 1 and for 7 days in Part 2	• Relationship between Day 1 AUC (0-24), Cmax, C24, and repeat-dose AUC (0-τ), Cmax and Cτ and GSK3640254 dose levels

Overall Design:

This is a Phase 2a, global, multicenter, randomized, double-blind (Sponsor-unblinded), placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability and PK/ pharmacodynamics (PD) of GSK3640254 over 10 days in study Part 1 and over 7 days in study Part 2 in ART-naïve HIV-1 infected adults who are termed "participants" in rest of this protocol.

This study will be conducted in two parts, separated to allow for an unblinded interim analysis performed after Part 1 (see Figure 1 Schematic for Study 208132).

Part 1 will evaluate two active doses of GSK3640254 in cohorts of 6 participants each.

- The 200 mg dose in Part 1 will be a well-tolerated dose of GSK3640254 based on the prior Phase I study (207187) that is predicted to provide at least 90% of the maximum anticipated effect for a maturation inhibitor on HIV-1 RNA reduction in a 10-day study. It is anticipated that this dose will be the highest dose to be tested in this study unless actual exposure in this population is lower than seen in healthy volunteers in studies 207187 and 208131.
- The 10 mg in Part 1 will target approximately fifty percent of the maximum anticipated effect on HIV-1 RNA reduction.

Part 1 will also include a cohort of 2 participants who will receive placebo. The justification for the use of a placebo control allows for blinded assessment of safety and tolerability. Since Investigators and patients will be blinded, any safety event (AE, lab abnormality, ECG abnormality, etc) will be evaluated and managed in the same fashion. Finally, the use of placebo control does allow for a comparison of antiviral effect between GSK3640254 and placebo.

Part 2 will evaluate up to three active doses of GSK3640254 (depending upon the data obtained in Part 1) in cohorts of 6 participants each.

- Part 2 doses may include one dose lower than the Part 1 10 mg dose, with the remaining doses between the range of Part 1 doses; one or two doses in Part 2 may be higher than the Part 1 200 mg dose if exposure in participants is lower than those observed from healthy participants in study 207187 and 208131.

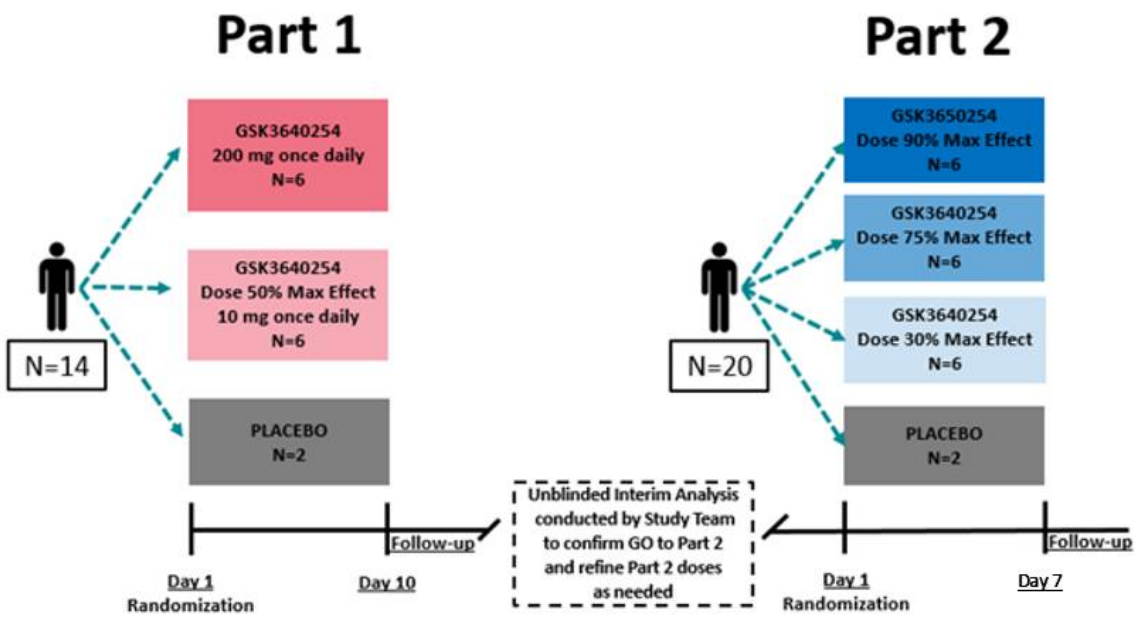
Part 2 will also include a cohort of 2 participants to receive placebo. The justification for the use of placebo in Part 2 is the same as Part 1 above.

In study Part 1, following a screening visit, qualified participants will be randomized within 14 days (up to 28 days in some cases) into one of the treatment arms, each consisting of a 10-day treatment and minimum of 8 visits over 17 days. Then participants will receive follow-up evaluations during approximately 1-2 weeks following the last dose.

In study Part 2, following a screening visit, qualified participants will be randomized within 14 days (up to 28 days in some cases) into one of the treatment arms, each consisting of a 7-day treatment and minimum of 6 visits over 8 days. Then participants will receive follow-up evaluations during approximately 3-5 days following the last dose.

This study will explore a wide dose range of GSK3640254. It will provide data to explore the safety, PK, and PK/PD relationship of GSK3640254 in HIV-1 infected participants and facilitate choice of doses for future studies.

Figure 1 Schematic for Study 208132



1. 10 and 200 mg once daily GSK3640254 mesylate salt
2. Part 1 safety/PK/viral load data will be evaluated at interim, prior to initiating other cohorts in Part 2, which are planned to run in a parallel, randomized fashion.
3. Part 2 doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Part 1.

Number of Participants:

A total of approximately 34 participants will be randomized into the 2-part trial.
Part 1 of the study will include approximately 14 randomized participants; Part 2 of the study will include approximately 20 randomized participants. In each study part, 6

participants will be enrolled in each of the GSK3640254 cohorts and 2 participants will be enrolled in each of the placebo cohorts, as shown in the Schematic for Study 208132.

It is estimated that approximately 68 participants will be screened in order to have 34 randomized and evaluable participants (screen failure rate of 50%).

If participants prematurely discontinue the study, additional participants may be randomized and assigned to the same cohort in consultation with the Investigator.

Treatment Groups and Duration:

The various treatment cohorts are shown in the Schematic for Study 208132.

All participants will be screened for eligibility before being randomized, preferably within 14 days, into a 10-day treatment period in Part 1 and into a 7-day treatment period in Part 2. The 14-day screening period may be extended to 28 days in some cases to allow receipt of all screening results and/or to accommodate scheduling.

A qualified participant will be randomized into the treatment phase of the study and will administer study treatments, once daily, from Day 1 through Day 10 in Part 1 and from Day 1 through Day 7 in Part 2. On Day 1, an appropriate number of bottles will be dispensed, with a supply sufficient to cover the entire treatment period. The blinded bottles will contain capsules of either the active dose or placebo. Dosing instructions will be indicated on each bottle. Participants will bring the bottles of study treatments to each visit, so that study treatment can be administered in the clinic after the study procedures have been performed.

Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories, with at least 120 calories from fat), that is required to be completed within 30 minutes prior to dosing. A moderate calorie and fat breakfast is planned to be similar to the following (additional meal suggestions will be included in the Study Reference Manual [SRM]):

- 2 slices of bread
- 10 g of butter
- 20 g of jam
- 15 g of cheese
- 175 mL of apple juice

Study treatments should be administered near the same time each morning, within a 2-hr window.

On days when the participant self-administers the study treatments, observed dosing with a site staff member may be achieved as locally permitted using various forms of video calling (when at all possible) such as FaceTime, Skype, WhatsApp.

Participants will then enter the post-dosing period:

Study Part 1:

There are 4 in-clinic visits in the Part 1 post-dosing period: 3 visits for PK and other assessments during the 7 days immediately following the last dose, and a final follow-up visit primarily for safety (e.g., to follow any AEs to resolution) approximately 8-14 days after the last dose, as shown in the Part 1 Schedule of Activities (SOA, Section 2). In Part 1, participants should not start other medicines and will not start ARVs during the post-dosing period until they have completed the final follow-up visit.

In the shortest course for Part 1, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in approximately 30 days (if, for example, only 10-14 days are needed for the screening period and the final follow-up visit is performed on Day 18). In the longest course for Part 1, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in 52 days (if, for example, 28 days are needed for the screening period and the final follow-up visit is performed on Day 24).

Study Part 2:

There are 2 in-clinic visits in the Part 2 post-dosing period: 1 visit for PK and other assessments on the day immediately following the last dose, and a final follow-up visit primarily for safety (e.g., to follow any AEs to resolution) 3-5 days after the last dose, as shown in the Part 2 Schedule of Activities (SOA, Section 2).

In Part 2, participants will start Investigator-selected, prescribed and provided cART immediately following the completion of the primary endpoint, i.e., the measurement of HIV-1 RNA on Day 8.

In the shortest course for Part 2, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow up visit) in approximately 24 days (if, for example, only 10-14 days are needed for the screening period and the final follow-up visit is performed on Day 10. In the longest course, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in 40 days (if, for example, 28 days are needed for the screening period and the final follow-up visit is performed on Day 12).

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Part 1 and Part 2 Screening

Procedure[1]	Screening (14 days[2] before Day 1)	Notes
Clinical Assessments		
Outpatient Visit	X	
Informed Consent	X	
Medical/medication/drug/alcohol history	X	
Prior anti-retroviral therapy	X	
Serious Adverse events (SAE) Assessment	X	Section 9.2
Center for Disease Control and Prevention (CDC) Classification	X	
Human immunodeficiency virus (HIV)-associated conditions assessment	X	
Height, Weight, Body Mass Index (BMI)	X	Section 9.4.1
Vital Signs	X	Section 9.4.2
Columbia Suicide Severity Rating Scale (C-SSRS) administration – *Baseline* form	X	Section 9.4.5
Clinical Procedures		
Electrocardiogram (ECG) (single reading)	X	Section 9.4.3
Pregnancy Test (Urine or Serum Human chorionic gonadotropin [β-hCG])	X	Section 9.2.6
Hematology/Chemistry/Urine	X	Section 9.4.4
Fasting Lipid Panel (approximately 8 hours)	X	Section 9.4.4
Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) serologies[3]	X	
Lymphocyte T-cell subsets (Cluster of designation 4 [CD4], CD8)	X	Section 9.1.2
HIV-1 Ribonucleic Acid (RNA)	X	Section 9.1.1
Drugs of Abuse	X	
Interactive Web Response System (IWRS) (RAMOS) activity[4]	X	

1. Procedures should be performed in this order: 1: ECG, Vital Signs, Blood Draws
2. Participants will be randomized within 14 days of the start of Screening; up to 28 days maximum may be allowed in some cases.
3. If test was otherwise performed within 3 months prior to first dose of study treatment, testing at Screening is not required.
4. Log in to RAMOS to complete a registration for participant ID assignment. If the participant fails screening, log in to RAMOS to register the participant as a Screen Fail.

2.2. Part 1 and Part 2 Treatment, Post-Dosing and Follow-up Periods

Study Part 1:

Procedure[1]	**Treatment Period Day 1 – Day 10**										**Post-Dosing Follow Up Period Day 11 – 17**			**Final Follow-up Day 18-24**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6, 7** Choose one day for the Clinic Visit 4. The other days will be virtual events.			**Day 8, 9, 10** Choose one day for the Clinic Visit 5. The other days will be virtual events.			**Day 11**	**Day 12**	**Day 13, 14, 15, 16 or 17**	**Day 18, 19, 20, 21, 22, 23 or 24**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Virtual**	**Clinic Visit 5**	**Virtual**	**Virtual**	**Clinic Visit 6**	**Clinic Visit 7**	**Clinic Visit 8**	**Clinic Visit 9**
Clinical Assessments														
Outpatient Visit[2]	X	X	X		X			X			X	X	X	X
Video/Phone Call				X		X	X		X	X				
Verify Inclusion/ Exclusion Criteria	X													
Medical/medication/drug/alcohol history	X													
Prior Anti-retroviral (ARV) Check	X													
CDC Classification	X													X

Procedure[1]	**Treatment Period Day 1 – Day 10**										**Post-Dosing Follow Up Period Day 11 – 17**			**Final Follow-up Day 18-24**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6, 7** Choose one day for the Clinic Visit 4. The other days will be virtual events.			**Day 8, 9, 10** Choose one day for the Clinic Visit 5. The other days will be virtual events.			**Day 11**	**Day 12**	**Day 13, 14, 15, 16 or 17**	**Day 18, 19, 20, 21, 22, 23 or 24**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Virtual**	**Clinic Visit 5**	**Virtual**	**Virtual**	**Clinic Visit 6**	**Clinic Visit 7**	**Clinic Visit 8**	**Clinic Visit 9**
HIV-associated conditions assessments[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event (AE)/SAE assessment[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, BMI and Physical exam[4]	X													
Vital Signs	X	X	X					X						X
C-SSRS Administration (*Since Last Visit* form)											X			

Procedure[1]	**Treatment Period Day 1 – Day 10**										**Post-Dosing Follow Up Period Day 11 – 17**			**Final Follow-up Day 18-24**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6, 7** Choose one day for the Clinic Visit 4. The other days will be virtual events.			**Day 8, 9, 10** Choose one day for the Clinic Visit 5. The other days will be virtual events.			**Day 11**	**Day 12**	**Day 13, 14, 15, 16 or 17**	**Day 18, 19, 20, 21, 22, 23 or 24**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Virtual**	**Clinic Visit 5**	**Virtual**	**Virtual**	**Clinic Visit 6**	**Clinic Visit 7**	**Clinic Visit 8**	**Clinic Visit 9**
Clinical Procedures														
12-lead ECG (triplicate reading, pre-dose; single readings at PK draws 2hr, 4hr, and 6hr)	X													
12-lead ECG (single reading, pre-dose at Visits 2 and 3)		X	X											X
12-lead ECG (single reading pre-dose and at PK draws 2hr, 4hr, and 6hr)								X						
Pharmacogenetics (PGX) Collection (if consented)	X													

Procedure[1]	**Treatment Period Day 1 – Day 10**										**Post-Dosing Follow Up Period Day 11 – 17**			**Final Follow-up Day 18-24**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6, 7** Choose one day for the Clinic Visit 4. The other days will be virtual events.			**Day 8, 9, 10** Choose one day for the Clinic Visit 5. The other days will be virtual events.			**Day 11**	**Day 12**	**Day 13, 14, 15, 16 or 17**	**Day 18, 19, 20, 21, 22, 23 or 24**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Virtual**	**Clinic Visit 5**	**Virtual**	**Virtual**	**Clinic Visit 6**	**Clinic Visit 7**	**Clinic Visit 8**	**Clinic Visit 9**
Hematology/Chemistry/Urine	X	X	X		X			X			X			X
Fasting Lipid Panel (approximately 8 hrs)	X										X			X
Lymphocyte T-cell subsets (CD4, CD8)	X										X			
Plasma for HIV-1 genotype/phenotype[5]	X	X	X		X			X			X	X	X	X
Plasma for storage[6]	X	X	X		X			X			X	X	X	X
HIV-1 RNA	X	X	X		X			X			X	X	X	X

Procedure[1]	**Treatment Period Day 1 – Day 10**										**Post-Dosing Follow Up Period Day 11 – 17**			**Final Follow-up Day 18-24**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6, 7** Choose one day for the Clinic Visit 4. The other days will be virtual events.			**Day 8, 9, 10** Choose one day for the Clinic Visit 5. The other days will be virtual events.			**Day 11**	**Day 12**	**Day 13, 14, 15, 16 or 17**	**Day 18, 19, 20, 21, 22, 23 or 24**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Virtual**	**Clinic Visit 5**	**Virtual**	**Virtual**	**Clinic Visit 6**	**Clinic Visit 7**	**Clinic Visit 8**	**Clinic Visit 9**
Single, Pharmacokinetic (PK) sample (pre-dose at Visits 3 and 4)			X		X						X[7]	X	X	
Intensive PK sampling[8] (with sample at 24hr time point the next morning)	X							X[9]						
Observed dosing with GSK3640254/placebo[3]	X	X	X	X	X	X	X	X	X	X				
IWRS (RAMOS) activity[10]	X													

1. Procedures should be performed in the following order: ECG, Vitals, Blood Draws, followed by dose administration.
2. The study requires 9 in-clinic visits. Flexibility is offered for Visits 3, 4, 5, 8 and 9. The visit schedule for each participant should be pre-planned to be sure weekend, work schedules and clinic hours are appropriately considered. No visit interval during the treatment period can be greater than 3 days.
3. These assessments must be conducted with a participant during each day indicated, to include the days when the participant is not in the clinic. This can be done in via phone, preferably via a visual method (as locally permitted) of Skype, Facetime, WhatsApp, et. al.
4. Physical Exam will include, at a minimum, assessments of the Skin, Heart, Lungs, and Abdomen (liver and spleen).
5. Genotypic/Phenotypic testing will be conducted on Day 1 and Day 11 samples, with other visits tested as appropriate.
6. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits. These samples will be used when needed, such as when samples are lost or where quantity is insufficient for testing. In the event samples are not used by study completion, they will be utilized for additional research on ARV resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing)
7. If the Intensive PK day occurs on Day 10, do not collect the Day 11 pre-dose PK sample (as it is redundant with the 24-hr PK collection (completing the sample set started on Day 10).
8. Intensive Plasma PK samples will be collected as outlined in Table 4 in Section 9.5
9. If Day 8 or 9 is the Clinic Visit 5 to include the Intensive PK collection, the participant must return the following day for the 24-hr PK collection, meal and dosing. The assessments to be done as indicated on what is a "virtual visit day" should be captured as a virtual visit, even if the questions are asked in the clinic.
10. Log in to RAMOS on Day 1 to randomize the participant and to receive blinded study treatment. Subsequently log-in to RAMOS for study treatment supply as needed. If a participant is discontinued from the study early, log in to RAMOS to record the discontinuation.

- The timing and number of planned study assessments, including safety, efficacy, pharmacokinetic, pharmacodynamic/biomarker 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 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Study Part 2:

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Clinical Assessments									
Outpatient Visit[2]	X	X	X		X		X	X	X
Video/Phone Call				X		X			
Verify Inclusion/ Exclusion Criteria	X								
Medical/medication/drug/alcohol history	X								
Prior Anti-retroviral (ARV) Check	X								
CDC Classification	X								X

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
HIV-associated conditions assessments[3]	X	X	X	X	X	X	X	X	X
Adverse event (AE)/SAE assessment[3]	X	X	X	X	X	X	X	X	X
Concomitant medication review[3]	X	X	X	X	X	X	X	X	X
Weight, BMI and Physical exam[4]	X								
Vital Signs	X	X	X				X		X
C-SSRS Administration (*Since Last Visit* form)								X	

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Clinical Procedures									
12-lead ECG (triplicate reading, done pre-dose; single readings at PK draws 2hr, 4hr, and 6hr)	X								
12-lead ECG (single reading, done pre-dose at Visits 2 and 3)		X	X						X
12-lead ECG (single reading done pre-dose and at PK draws 2hr, 4hr, and 6hr)							X		

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Pharmacogenetics (PGX) Collection (if consented)	X								
Hematology/Chemistry/Urine	X	X	X		X		X	X	X
Fasting Lipid Panel (approximately 8 hrs)	X							X	X
Lymphocyte T-cell subsets (CD4, CD8)	X							X	
Plasma for HIV-1 genotype/phenotype[5]	X	X	X		X		X	X	
Plasma for storage[6]	X	X	X		X		X	X	X

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
HIV-1 RNA	X	X	X		X		X	X	X
Single, Pharmacokinetic (PK) sample done pre-dose			X		X				
Intensive PK sampling (to include the 24hr samples drawn the next day)	X						X		
Observed dosing with GSK3640254 /placebo[3]	X	X	X	X	X	X	X		

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Observed dosing with Investigator-selected, prescribed and provided CART, and eCRF completion								X	
IWRS (RAMOS) activity[8]	X								

1. Procedures should be performed in the following order: ECG, Vitals, Blood Draws, followed by dose administration.
2. The study requires 7 in-clinic visits. Flexibility is offered for Visits 3, 4 and 7. The visit schedule for each participant should be pre-planned to be sure weekend, work schedules and clinic hours are appropriately considered. No visit interval during the treatment period can be greater than 3 days.
3. These assessments must be conducted with a participant during each day indicated, to include the days when the participant is not in the clinic. This can be done in via phone, preferably via a visual method (as locally permitted) of Skype, Facetime, WhatsApp, et. al.
4. Physical Exam will include, at a minimum, assessments of the Skin, Heart, Lungs, and Abdomen (liver and spleen).
5. Genotypic/Phenotypic testing will be conducted on Day 1 and Day 8 samples, with other visits tested as appropriate.
6. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits. These samples will be used when needed, such as when samples are lost or where quantity is insufficient for testing. In the event samples are not used by study completion, they will be utilized for additional research on ARV resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing)
7. Intensive Plasma PK samples will be collected as outlined in Table 4 in Section 9.5
8. Log in to RAMOS on Day 1 to dispense blinded study treatment. Subsequently log-in to RAMOS for study treatment supply as needed. If a participant is discontinued from the study early, log in to RAMOS to record the discontinuation.

- The timing and number of planned study assessments, including safety, efficacy, pharmacokinetic, pharmacodynamic/biomarker 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 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF

3. INTRODUCTION

GSK3640254 is a next-generation HIV-1 Maturation Inhibitor (MI); this novel class of anti-HIV-1 medicines prevents the maturation of HIV-1 virions by binding near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton (kDa) HIV capsid (CA) protein p24 (CA [p24]) and spacer peptide 1 (SP1). Blockage at this step results in the release of immature non-infectious virus particles. GSK3640254 is potent and has a broad pan-genotypic spectrum in vitro. There are no Maturation Inhibitors (MIs) approved for the treatment of HIV infection.

3.1. Study Rationale

The proposed Study 208132 is a proof of concept (POC), randomized double blind (Sponsor-unblinded) study to characterize antiviral activity, safety/tolerability, PK, and the relationship between PK and antiviral activity of GSK3640254 given once daily (QD), administered across a range of doses over 10 days in study Part 1 and over 7 days in study Part 2 in HIV-1 infected treatment-naïve adults. To minimize the number of participants exposed to suboptimal or redundant doses, a two-part, adaptive and dose-ranging design is applied in this study. This two-part, adaptive design will allow an early understanding of the potential of GSK3640254, while not exposing HIV-infected participants to longer courses and possible development of resistance. Data from this study will be utilized to select doses for further studies in Phase 2b.

3.2. Background

GSK3640254 is an HIV MI which is improved over prior developmental MIs in the following ways: (1) it exhibits significantly improved pangenotypic 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 GI tolerability; and (5) it has a projected lower once-daily human dose (see Dose Justification, Section 5.5). Summaries of the pre-clinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GSK Document Number 2018N379610_00]

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

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 gastrointestinal (GI) intolerability (specifically Grade 1-2 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. GI AEs were also previously observed in healthy participants in Phase 1 studies with varying doses, durations, and formulations of GSK3532795. In all three studies, the most common GI AEs were abdominal pain and diarrhea.

Aside from mild-moderate GI intolerability, two serious adverse events (SAEs) occurred in the Phase I Thorough QT study AI468044/206220 [CSR, BMS] at supra-therapeutic doses: one healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The two participants received GSK3532795 240 mg twice daily (BID) and 240 mg QD for 3 days 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).

3.2.2. Preliminary Safety and PK Data in Study 207187

The First Time in Human Clinical Trial's (207187) primary objective 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 1-700 mg) and 58 in the multiple ascending dose (MAD, 50-320 mg QD for 14 days). A comprehensive summary of results is described in the Investigator Brochure [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 have been reported. There were 4 AEs leading to discontinuation. Only one of these 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 once daily/a topical steroid cream with resolution. The other three AEs occurred in SAD portion of the study (depression in a subject who received placebo and two subjects with viral infection).

There were 9 subjects with 12 AEs assessed as related to study medication by the principle 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, they had 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 x 23 x 36 mm. A follow up MRI and liver chemistries were normal. This subject also had three unrelated AEs during the course of an isolated increased ALT: musculoskeletal stiffness, contact dermatitis, and headache. All other related AEs are described in the Investigator's Brochure (IB) [GSK Document Number 2018N379610_00] and the Study Synopsis [GSK Document Number 2018N375461_00].

In the SAD, seventeen 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, 43 subjects experienced 126 individual AEs (123 Grade 1; 3 Grade 2). The 3 Grade 2 AEs were headache (one related and one 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 ms or increases >60 ms from Baseline) observed for any participant in the SAD or MAD. A cardiodynamic evaluation of healthy subjects in the MAD portion of Study 207187 (placebo or GSK3640254 dose range 50 to 320 mg daily for 14 days) was performed. Serial ECGs were extracted from continuous Holter monitors at time-matched baseline on Day -1 and for approximately 24 hours post-dose on Days 1 and 14. In the concentration-QTc analysis, a final model with a treatment effect-specific intercept reasonably represented the data. The slope of the concentration-QTc relationship was 0.004 ms per ng/mL (90% confidence interval [CI]: 0.0023 to 0.0048) with a small treatment effect-specific intercept of -0.9 ms (90% CI: -4.47 to 2.69). The QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD; note, the maximum dose used in Part 1 of this study, 208132, is 200 mg QD). Finally, 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 mg to 700 mg administered after a moderate calorie and fat breakfast show GSK3640254 is slowly absorbed with a median Tmax observed between 3-4.5 hours after dosing with a moderate fat breakfast and slowly eliminated with a mean half-life ranging from 22-26 hours. In general, exposure (maximum observed concentration [Cmax] and area under the curve [AUC]) increased in a close-to-dose-proportional manner from 1 mg to 400 mg with no further increase in exposure at 700 mg.

Repeat dose preliminary PK parameter following once-daily administration of 50 to 320 mg QD for 14 days were determined on Day 1 and Day 14 and show 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(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].

3.2.3. Preliminary Safety and PK Data in Study 208131

The FTIH Study 207187 uses 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 cross-over design, conducted in 14 healthy subjects in the UK, 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 have completed dosing and the blinded preliminary safety data from Study 208131 shows a total of 11 AEs (all Grade 1). Two were related: Headache. The most common AE was Headache (3 instances). There were three Gastrointestinal 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 107% and 110% based on AUC(0-∞) and Cmax respectively. Due to the similarity in exposure between the Bis-hydrochloride and Mesylate salt capsules, no dose adjustment is required for study 208132.

3.2.4. Justification for Part 2 Treatment Duration and Initiation of cART

Data from Part 1 showed a decline in HIV-1 RNA and reasonable PK profile. There were no clinically significant trends in AEs, vital signs, ECG findings, or chemistry or haematology laboratory abnormalities across dosing arms. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on Day 11 (after 10 days of receiving GSK3640254 monotherapy). Additionally, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed at Day 11 as there is no known cross-resistance between maturation inhibitors and other classes of ARVs. Genotypic analysis of samples at Clinic Visit 5 (Study Day 8 or 9) revealed no treatment emergent resistance. As a result, VH made two substantial changes to decrease the risk of treatment emergent resistance to participants in study Part 2: 1) decrease the duration of monotherapy from 10 days to 7 days (based on the interim genotypic analysis), and 2) immediately start Investigator-selected cART at the completion of monotherapy at the Part 2 primary endpoint (HIV-1 RNA measured on Day 8).

3.3. Benefit/Risk Assessment

Based upon pre-clinical and clinical studies with the prior MI GSK3532795 and the current molecule GSK3640254, the major risks are GI intolerability (e.g. abdominal pain and diarrhoea) and toxicity, prolongation of QTc, neuropsychiatric safety, and treatment

emergent resistance to GSK3640254. If present, preclinical GI toxicity findings (e.g. single cell parietal cell necrosis) in subjects would be minimal and not be persistent upon discontinuation of GSK3640254 after 7 days of dosing. The risk of GI intolerability and neuropsychiatric safety is described in Section 3.3.1. The risk for QTc prolongation is described below in Section 3.3.1 where one pre-clinical study did show one dog with an increased QTc interval when given a single dose of GSK3640254. As described in Section 3.2.2, a cardiodynamic analysis of healthy subjects in Study 207187 was conducted. A final model from the MAD data showed a QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD; note, 200 mg QD was the maximum dose used in Part 1 of this study 208132). Importantly, there were no abnormal clinically significant arrhythmias or QTc prolongations (values >500 ms or increases >60 ms from Baseline) in Study 207187. This study contains specific cardiac exclusion criteria, has ECG monitoring (at Tmax once GSK3640254 attains steady state concentration), and has QTcF based stopping criteria.

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, and neuropsychiatric safety), this clinical trial will include participants who will receive clinical, laboratory, and ECG assessments during their participation in the trial. The protocol will also include a psychological assessment (C-SSRS) to be administered by the investigator or a clinician (or qualified designee) at screening and the end of the trial. Finally, daily AE enquiry will also include a question as to a participant's mental health and mood. Participants with any pre-existing psychiatric condition or positive (abnormal) response on the C-SSRS confirmed by the investigator/ qualified designee will be excluded (and urgent evaluation by a psychiatrist will be arranged).

VH has assessed this study for any risks that may be posed to participants taking part. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMEA) guidance on strategies to identify and mitigate risks for clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/XX).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3640254 may be found in the most current version of the Investigator's Brochure [GSK Document Number 2018N379610_00].

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3640254]		
Cardiovascular (QT prolongation)	Pre-clinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and Ltype calcium channel currents recorded from HEK 293 cells stably transfected with 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 one dog given 17 mg/kg. Later, there were no GSK3640254-related effects on ECG parameters in dogs given up to 25 mg/kg/day for 4 weeks. In the first time in human study 207187, no participant exhibited QTc change from baseline >60 ms or QTc >500 ms. As described in Section 3.2.2, in the concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD).	Protocol exclusion criteria based on screening ECG parameters and cardiac medical history (see Section 6.2). Participants will have ECG monitoring during the course of the study (see SOA table) with QTc stopping criteria (see Section 8.1.2).
Gastrointestinal intolerability and toxicity	Clinical signs indicative of gastrointestinal intolerability (sporadic vomiting and abnormal faeces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms (see Section 6.2) Participants will undergo continuous evaluation for adverse events during their participation in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. The rates of GI AEs from the FTIH and RBA clinical trials (described above) are summarized in their respective synopses and the current Investigator Brochure.	the trial; there are clinical stopping criteria based upon intensity of treatment-emergent AEs (see Section 8.1.3). Finally, a GI toxicity evaluation and monitoring plan is available to guide the principal investigator (PI) should GI AEs emerge (see Section 9.4.6).
Neurologic/psychiatric safety	Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. From a Neurologic and Psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. The rates of Neurologic and Psychiatric AEs from the	Protocol exclusion criterion based on any preexisting psychiatric condition (including results of psychological assessment) for patients. Participants will have psychological assessment via a clinician (or qualified designee) administered C-SSRS in the study and will be included given no positive (abnormal) response. Continuous evaluation for adverse events during their participation in the trial including daily direct AE enquiry; The C-SSRS will also be administered after the treatment phase of the study. In the event of a positive (abnormal) response confirmed by the investigator, the patient will discontinue from the trial and the Principal Investigator/ Sub-Investigator (PI/SI) will arrange for urgent

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	FTIH and RBA clinical trials (described above) are summarized in their respective synopses and the current Investigator's Brochure.	specialist psychiatric evaluation and management. Guidance for the PI on the management of emergent psychiatric symptoms are available (see Section 9.4.5) Finally, there are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 8.1.3).
HIV-1 Infection/Patient population		
HIV Resistance to GSK3640254	HIV-1 genotypic and phenotypic changes due to GSK3640254 monotherapy. Data from Part 1 showed a decline in HIV-1 RNA and reasonable PK profile. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on or after Day 11 (after 10 days of receiving GSK3640254 monotherapy). Additionally, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed at Day 11 as there is no known cross-resistance between maturation inhibitors and other classes of ARVs. Genotypic analysis of samples at Clinic Visit 5 (Study Day 8 or 9) revealed no treatment emergent resistance.	Dosing is limited to 10 days of monotherapy in Part 1 to reduce the risk of emergent drug resistance, and additionally limited to 7 days of monotherapy in Part 2 to further reduce the risk of emergent MI drug resistance based on the genotypic analysis of the interim samples from Part 1. There are no commercially available/approved MIs nor is there evidence of cross-class resistance (e.g. protease inhibitors) therefore dosing with GSK3640254 will not interfere with selection of a cART regimen at the completion of the entire study (for Part 1) or the completion of the monotherapy portion of the study (Part 2). Strict adherence to protocol criteria around concurrent meds.

3.3.2. Benefit Assessment

This study in HIV-1 infected but otherwise healthy participants is a short-term monotherapy design. There is no expected longer-term anti-HIV benefit to administration of GSK3640254.

3.3.3. Overall Benefit:Risk Conclusion

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy participants at the proposed GSK3640254 doses, for 10 days in Part 1 and for 7 days in Part 2, is predicted to be low and manageable. Mean exposures at the highest dose studied are not projected to exceed lowest observed adverse effect level (LOAEL) values obtained in chronic toxicology studies, further reducing potential risk.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of GSK3640254 in HIV-1-infected participants during 10 days of monotherapy in Part 1 and during 7 days of monotherapy in Part 2	• Maximum change from baseline (Day 1) in plasma HIV-1 RNA
Secondary	
• To assess the safety and tolerability of GSK3640254 when administered as monotherapy over 10 days in Part 1 and over 7 days in Part 2 in HIV-1 infected participants	• GSK3640254 safety and tolerability parameters: adverse events (AE); post-baseline values and changes over time of clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters
• To characterize the pharmacokinetics of GSK3640254 dosing for 10 days in Part 1 and for 7 days in Part 2 in HIV-1 infected patients	• GSK3640254 PK parameters at the following dose administration: Day 1: area under the plasma concentration time curve from zero to 24 (AUC [0-24]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag) Following repeat administration: Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC[0-τ]), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval ($C\tau$), apparent terminal phase half-life (t1/2), and apparent oral clearance (CL/F), if data permit.

Objectives	Endpoints
• To explore the relationship between GSK3640254 exposure and change in plasma HIV-1 RNA	• GSK3640254 repeat-dose PK parameters AUC(0-τ), Cmax, Cτ with maximum HIV-1 RNA change from baseline
• To estimate GSK3640254 accumulation following administration of GSK3640254 for 10 days in Part 1 and for 7 days in Part 2 in HIV-1 infected patients.	• Accumulation: GSK3640254 PK accumulation ratios (R): repeat -dose AUC (0-τ), Cmax, and Cτ compared to Day 1 AUC (0-24), Cmax, C24, respectively
• To examine dose proportionality of GSK3640254 PK parameters following dosing for 10 days in Part 1 and following dosing for 7 days in Part 2	• Relationship between Day 1 AUC (0-24), Cmax, C24, and repeat-dose AUC (0-τ), Cmax and Cτ and GSK3640254 dose levels
Exploratory	
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days in Part 1 and over 7 days in Part 2 and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To assess attainment of steady state following administration of GSK3640254 for 10 days in Part 1 and for 7 days in Part 2 in HIV-1 infected patients.	• Steady State: pre-morning dose concentrations (C0) on Day 2 through Day 10 Cτ (Day 11) in Part 1 and on Day 2 through Day 7 Cτ (Day 8)
• To assess the immunologic effects of GSK3640254 when administered over 10 days in Part 1 and over 7 days in Part 2 in HIV-1 infected adults	• Change from baseline in CD4+ T-cell count to Day 11 in Part 1 and to Day 8 in Part 2
• To explore the relationship between GSK3640254 exposure and safety or immunologic parameters, if appropriate	• GSK3640254 repeat-dose PK parameters: AUC (0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count in Part 1 and with Day 8 change from baseline in CD4+ cell count in Part 2
Note: Other exploratory objectives and endpoints may be specified in the Reporting and Analysis Plan (RAP).	

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2a, global, multicenter, double-blind (Sponsor-unblinded), randomized, placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability, PK and PD of GSK3640254 over 10 days in study Part 1 and over 7 days in study Part 2 in ART-naïve HIV-1 infected adults.

This study will be conducted in two parts, separated to allow for an informal interim analysis performed after Part 1 (see Figure 1 Schematic for Study 208132).

Part 1 will include approximately 14 randomized participants and will evaluate two active doses of GSK3640254 in cohorts of 6 participants each.

- The Part 1 200 mg dose was a well-tolerated dose of GSK3640254 based on the prior Phase I study (207187) that is predicted to provide at least 90% of the maximum anticipated effect for a maturation inhibitor on HIV-1 RNA reduction in a 10-day study. It is anticipated that this dose will be the highest dose to be tested in this study unless actual exposure in this population is lower than seen in healthy volunteers in studies 207187 and 208131.
- The Part 1 10 mg dose will target approximately fifty percent of the maximum anticipated effect on HIV-1 RNA reduction.

Part 1 will also include a cohort of 2 participants who will receive placebo. The justification for the use of a placebo control allows for blinded assessment of safety and tolerability. Since Investigators and patients will be blinded, any safety event (AE, lab abnormality, ECG abnormality, etc) will be evaluated and managed in the same fashion. Finally, the use of placebo control does allow for a comparison of antiviral effect between GSK3640254 and placebo.

Part 2 will include approximately 20 randomized participants and will evaluate up to three active doses of GSK3640254 (depending upon the data obtained in Part 1) in cohorts of 6 participants each.

- Part 2 doses may include one dose lower than the low Part 1 dose, with the remaining doses between the range of Part 1 doses; one or two doses in Part 2 may be higher than the high dose in Part 1 if exposure in participants is lower than those observed from healthy participants in study 207187 and 208131.

Part 2 will also include a cohort of 2 participants to receive placebo. The justification for the use of placebo in Part 2 is the same as Part 1 above.

5.1.1. Treatment Groups and Duration

5.1.1.1. Screening Phase

All participants will be screened for eligibility before being randomized, preferably within 14 days, into a 10-day treatment period in study Part 1 and into a 7-day treatment period on study Part 2. Randomization may occur as soon as all Screening procedures have been completed and results are available and on file. The 14-day screening period may be extended (in some cases) to 28 days to allow receipt of all Screening assessment results and to accommodate scheduling.

5.1.1.2. Treatment Phase and Follow-up Period

Part 1:

Participants will be required to attend 9 in-clinic visits throughout the duration of the study in Part 1. Participant and Investigators will design a patient-centric visit schedule

based on the optionality presented in the Part 1 Schedule of Assessments (SOA; Section 2) to accommodate the 9 required visits over the (maximum) 24-day study period, and such that no visit interval exceeds more than 3 days.

Part 2:

Participants will be required to attend 7 in-clinic visits throughout the duration of the study in Part 2. Participant and Investigators will design a patient-centric visit schedule based on the optionality presented in the Part 2 Schedule of Assessments (SOA; Section 2) to accommodate the 7 required visits over the (maximum) 12-day study period, and such that no visit interval exceeds more than 3 days.

Treatment Phase: Day 1 – Day 10 in Part 1 and Day 1 – Day 7 in Part 2:

On Day 1, an appropriate number of bottles of study treatments will be dispensed with supply sufficient to cover the entire treatment period. The blinded bottles will contain capsules of either the active dose or placebo. Each bottle will indicate dosing instructions. Participants will bring the bottles of study treatments to each visit, so that they can be administered after the study procedures have been performed.

Participants will report to the clinic for visits in the morning of the days selected for each of the 5 visits in the treatment phase. Participants will arrive each day, with their study treatment container(s) and prior to administration of the morning dose, for safety and lab assessments, including ECGs and blood draws, as described in the SOA. Participants will be given morning doses in the clinic at each visit. On days when an in-clinic visit is not required, doses can be self-administered, and during observation by a site staff member using various forms of video calling (when at all possible and locally permitted) such as FaceTime, Skype, WhatsApp.

Two, serial, intensive blood PK sample collections will be done on Clinic Visit 1 and on Clinic Visit 5 (up to 24 hours post-morning dose). Participants will be required to fast for at least 8 hours [overnight] prior to the morning check-in for the intensive PK sampling visits. Participants will be required to stay in the clinic until all specified assessments are completed (12 hours post-dose). Participants will be required to return to the clinic the following morning to allow for the blood sampling at the 24-hr time point.

Study treatments should be administered near the same time each morning, within a 2-hr window.

Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories, with at least 120 calories from fat), that is required to be completed within 30 minutes just prior to dosing. A moderate calorie and fat breakfast is planned to be similar to the following (with additional meal suggestions in will be included in the Study Reference Manual [SRM]):

- 2 slices of bread
- 10 g of butter
- 20 gr of jam

- 15 g of cheese
- 175 mL of apple juice

Follow-up Visits

Part 1:

Follow-up Visits Day 11-17 and Final Follow-up Visit Day 18-24

Participants should not start other medicines and will not start ARVs during the post-dosing follow-up period until after the final follow-up visit has been completed.

Participants will return to the clinic in the post-dosing period for 4 visits (Visits 6-9).
- Three visits will be performed within the 7 days immediately following the dosing period for PK and measurement of assessments as shown in the SOA (Section 2).
- A final follow-up visit, to be performed approximately 8-14 days after the last dose, will be primarily for safety (e.g., to follow any AEs to resolution).

If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the participant for assessment of adverse events.

Part 2:

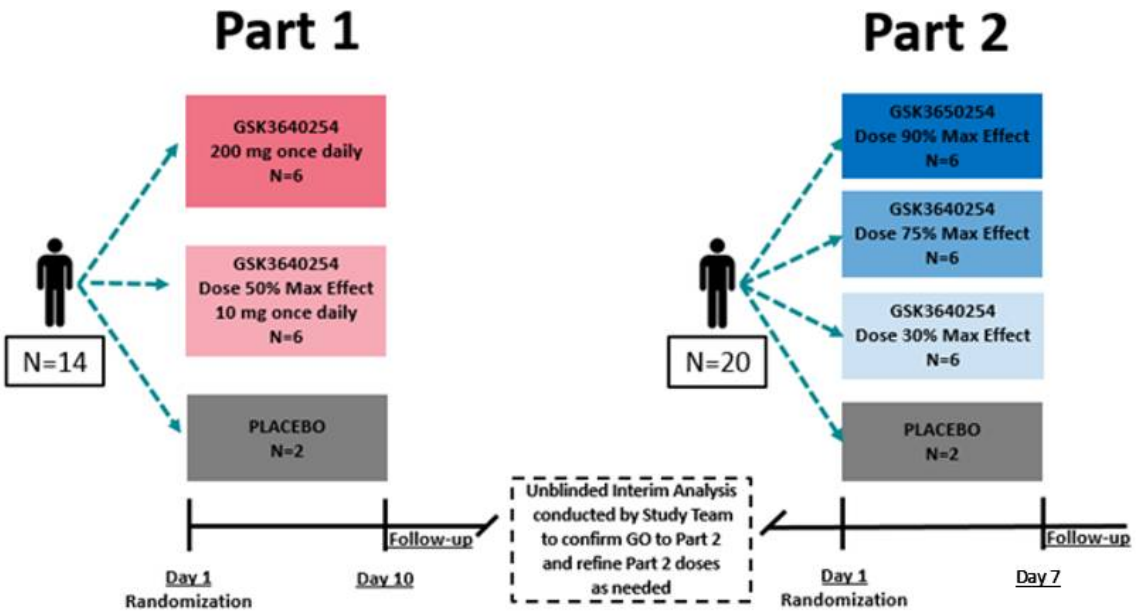
Follow-up Visit Day 8 and Final Follow-up Visit Day 10-12

Participants should start Investigator-selected, prescribed and provided cART immediately in the post-dosing period on Day 8, after the blood collection is performed.

Participants will return to the clinic in the post-dosing period for 2 visits (Visits 6 and 7).
- One visit will be performed on the day immediately following the dosing period for PK and measurement of assessments as shown in the SOA (Section 2).
- A final follow-up visit, to be performed approximately 3-5 days after the last dose, will be primarily for safety (e.g., to follow any AEs to resolution).

If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the participant for assessment of adverse events.

Schematic for Study 208132



1. Mesylate Dose equivalent to 10 and 200 mg once daily bis-HCL
2. Part 1 safety/PK/viral load data will be evaluated at interim, prior to initiating other cohorts in Part 2, which are planned to run in a parallel, randomized fashion.
3. Part 2 doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Part 1.

5.2. Number of Participants

A total of approximately 34 participants will be randomized into the trial. Approximately 14 participants will be randomized in Part 1 of the study, and approximately 20 participants will be randomized in Part 2 of the study. Six participants will be enrolled in each of the active dose cohorts and 2 participants will be enrolled in each of the placebo cohorts.

Additional participants/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If participants prematurely discontinue the study, additional participants may be randomized and assigned to the same cohort in consultation with the Investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if the participant has completed all phases of the study including the last scheduled procedures shown in the SOA.

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

5.4. Scientific Rationale for Study Design

Antiviral potency of a novel HIV drug is typically established in a short-course monotherapy study in HIV infected participants. There is precedent for this across a number of classes of ART drugs.

Understanding the uncertainties over the inherent potency of GSK3640254 in inhibiting the HIV maturation process is a key objective for the GSK3640254 program. This two-part, adaptive design will allow an early understanding of the potential of GSK3640254, while not exposing HIV-infected participants to longer courses of what may be suboptimal or redundant doses and possible development of resistance. The two-part design will allow for an interim evaluation of the data to refine the doses to be studied in Part 2, as needed, therefore ensuring that the doses are adequate to characterize the dose-exposure-relationship for GSK3640254.

All doses of GSK3640254 in this study will be administered in the fed state, with dosing occurring within 30 minutes of completing a moderate fat meal (i.e. at least 400 calories, at least 120 calories from fat). Data with a previous MI, GSK3532795, demonstrated that food was necessary to achieve dose proportional PK and target efficacious concentrations. Given the structural similarities, including solubility limitations, between GSK3532795 and GSK3640254, current clinical studies evaluated the safety, tolerability, and PK of GSK3640254 after administration of a moderate fat meal.

In Study 207187 (SAD/MAD), doses up to 320mg QD for 14 days were evaluated in a repeated dose cohort. The dose of 320 mg QD is potentially 4 times the minimally anticipated effective dose of 80 mg predicted based on the emerging PK in healthy volunteers and the target trough concentration based on virology data. As described in Section 3.2.2, the current Investigator's Brochure, and the Study 207187 synopsis, doses up to 320 mg QD for 14 days were generally well tolerated. Doses up to exposure seen at 200 mg QD in healthy volunteers will be used in this study of HIV-1 infected patients to understand the relationship between GSK3640254 exposures and efficacy, duration of response, and development of genotypic and phenotypic changes.

5.5. Dose Justification

The doses to be used in this study have been defined to adequately described the dose-exposure-response of GSK3640254 in treatment-naïve HIV patients. The doses were selected as to approximately provide a median effect of 30, 50, 75, 90 and 95% of the maximum anticipated effect on HIV-1 RNA for an MI drug in a 7-day or 10-day study.

5.5.1. Dose Justification for Part 1

Historical information from the 10-day POC study conducted with the prior MI compound, GSK3532795, was obtained. In that study, a simple effect, at the maximum (Emax) model described the relationship between the individual maximum viral load decrease and the individual inhibitory quotient (IQ). The IQ was computed by dividing the steady-state trough concentration by the individual protein binding adjusted EC90 (PBAEC90). The IQ providing 50% of the maximum effect was 1.93.

Based on the FTIH study for GSK3640254, the pharmacokinetics of GSK3640254 were described by a two-compartment model with between subject variabilities on the elimination clearance, the central volume of distribution and the absorption rate constant.

The population PK model of GSK3640254, including parameter uncertainty, was integrated with the PK/ Pharmacodynamic (PD) model of GSK3532795 and the distribution of PBAEC90 obtained with GSK3640254 in in vitro experiment with 36 Gag/PR genotyped viruses (e.g. mean of 19.1 ng/mL with CV% of 33%). It was assumed that the PK of GSK3640254 in treatment-naïve HIV patients will be similar to that seen in healthy participants. One thousand trials with 6 participants per dose level were simulated to generate, for each individual, the anticipated percent of maximum effect. Simulations were then summarized by computing the median percent of maximum effect for each dose and trial and then further computing the median and 95% prediction interval around the median for each dose across the trials. The simulations are summarized in Table 1.

Table 1 Predicted median and 95% prediction interval for median percent of maximum effect for different doses (1000 trials with N=6 per dose level)

Dose (mg)	2.5th Percentile	Median	97.5th Percentile
5	14.2	31.4	53.5
10	24.8	47.6	69.7
15	33	57.4	77.5
20	39.4	64.1	82.1
25	44.4	69	85.1
30	48.5	72.7	87.2
40	55.5	78	90.1
80	71.1	87.6	94.8
100	75.4	89.8	95.8
200	85.9	94.6	97.8

Based on these simulations and on similar relative bioavailability between the Bis-hydrochloride salt (used in the 207187 FTIH study) and mesylate salt capsules shown in study 208131, Part 1 doses will be 10 mg and 200 mg to respectively approximately provide 50% and 95% of maximum effect.

5.5.2. Dose Justification for Part 2

It is predicted that Part 2 doses would be 5 mg, 40 mg, and 100 mg to respectively provide approximately 30%, 75% and 90% of maximum effect but these doses and target

effects will be evaluated at the end of Part 1. An evaluation and unblinded interim analysis of GSK3640254 safety, tolerability, PK and antiviral activity will occur after all participants of Part 1 complete their Day 12 visit. The detailed decision rules are illustrated in Section 10.3.1.

Doses higher than 200 mg QD may be explored in Part 2, in the case that the overall PK exposure is lower in HIV infected participants relative to healthy participants. The higher dose(s) would be designed to not exceed the exposure seen in healthy participants at 200 mg QD.

Predicted steady-state exposures for 200 mg QD are essentially equal to the no-observed-adverse-effect-level (NOAEL) exposure in a 4-Week oral toxicity study in rats, although no NOAEL was identified in dogs for gastrointestinal intolerability and minimal effects of parietal cells following 4 weeks of dosing. Predicted steady-state exposures over the proposed dose range along with fold cover to rat and dog LOAEL exposures, the lowest exposures where minimal, reversible effects on parietal and/or chief cells were identified, and mean IQ values for different GSK3640254 doses are presented in Table 2.

Table 2 Predicted Mean Steady-State GSK3640254 Cmax, AUC(0-24), C24, and IQ, Following Repeated Dose Administration with Fold Cover to rat and dog LOAEL

Doses (mg)	Cmax, ng/mL[1]	AUC(0-24), ng.h/mL	C24, ng/mL	IQ[2]	Fold cover rat:human Cmax[3]	Fold cover rat:human AUC(0-24)	Fold cover dog:human Cmax[3]	Fold cover dog:human AUC(0-24)
5	61	937	30	1.59	64.7	65.2	68.1	78.3
10	113	1736	56	2.94	34.9	35.2	36.7	42.2
40	389	5962	193	10.1	10.2	10.2	10.7	12.3
100	879	13475	436	22.8	4.5	4.5	4.7	5.4
200	1629	24972	809	42.3	2.4	2.4	2.6	2.9

1. Predicted mean values based on linear regression analyses of preliminary Day 14 data in Study 207187 available by 01-June-2018.
2. Mean IQs derived from predicted mean C24/ mean PBAEC90 of 19.1 ng/mL. The PBAEC90 for the triple variant is approximately 1.9-fold higher or 36.7 ng/mL.
3. A NOAEL was achieved in 1-month study in rats given 10mg/kg/day (AUC(0-24) of 22400 ng.h/mL and Cmax of 2370 ng/mL on Day 28). Lowest LOAEL exposure was in 1-month study in rats given 30 mg/kg/day (AUC (0-24) of 61100 ng.h/mL and Cmax of 3950 ng/mL on Day 28). The LOAEL in 1-month study in dogs was 1 mg/kg/day (AUC (0-24) of 73300 ng.h/mL and Cmax of 4160 ng/mL on Day 28).

C24 = trough concentration at the end of the dosing interval, IQ= inhibitory quotient.

6. STUDY POPULATION

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

Repeat testing of certain lab parameters within a single Screening period is allowed as indicated in the following sections. Participants may be screened twice.

6.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy (other than HIV infection) as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, laboratory tests, and cardiac monitoring.

3. Screening CD4+ T-cell count ≥350 cells/mm3

4. Documented HIV infection and Screening plasma HIV-1 RNA ≥5000 copies/mL. A single repeat of this test is allowed within a single Screening period to determine eligibility.

5. Treatment-naïve: No ARVs (in combination or monotherapy) received after the diagnosis of HIV-1 infection.

Weight

6. 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 18.5-31.0 kg/m^2 (inclusive).

Sex

7. Male or female:

a. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

Informed Consent

8. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and stated in the protocol.

Other

9. **For participants enrolled in France**: a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

10. Participant must be willing and able to start cART on Study Day 8 (except in the case of early termination, clinically relevant AE/SAE, lab abnormality, the withdrawal of consent, lost to follow-up, etc., where circumstances could dictate otherwise).

6.2. Exclusion Criteria

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

Medical Conditions

1. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to starting study treatment

2. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study treatment AND positive on reflex to Hepatitis C RNA

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained (central lab will automatically reflex to HCV RNA on positive HCVAb)

3. Alanine aminotransferase (ALT) >2 x upper limit of normal (ULN). A single repeat of ALT is allowed within a single Screening period to determine eligibility.

4. Bilirubin >1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

5. Subjects with primary HIV infection, evidenced by acute retroviral syndrome (e.g., fever, malaise, fatigue, etc) and/or evidence of recent (within 3 months) documented viremia without antibody production and/or evidence of recent (within 3 months) documented seroconversion.

6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);

7. A pre-existing condition interfering with normal gastrointestinal anatomy or motility (e.g., gastroesophageal reflux disease [GERD], 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 treatment.

8. Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.

9. Any Grade 2-4 laboratory abnormality at Screen, 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 lab abnormality is allowed within a single Screening period to determine eligibility.

10. 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.

11. 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.

12. 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.

13. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.

Prior/Concomitant Therapy

14. 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.

Prior/Concurrent Clinical Study Experience

15. The participant has participated in a clinical trial and has received an investigational product within the 30 days prior to the first dosing day in the current study.

Diagnostic assessments

16. Any positive (abnormal) response confirmed by the investigator on a Screening clinician- (or qualified designee-) administered C-SSRS.

17. Any positive result for illicit drug use (e.g., cocaine, heroin) at Screening. A positive screen for marijuana is not exclusionary, though if positive for THC, see Section 6.3.2 for guidance to be given to the participant.

18. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.

19. Exposure to more than four new investigational drugs or vaccines within 12 months prior to the first dosing day.

20. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days of study drug administration or anticipated need for such treatment within the study.

21. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; or other localized malignancies require agreement between the investigator and the study medical monitor for inclusion of the subject prior to randomization.

Treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (such as hydroxyurea or foscarnet) within 30 days of study drug administration.

22. An active Center for Disease Control and Prevention (CDC) Category C disease except cutaneous Kaposi's sarcoma not requiring systemic therapy during the trial.

23. Treatment with any vaccine within 30 days prior to receiving study medication.

24. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate[1]	<45 or >100 bpm	<50 or >100 bpm
PR Interval	<120 or >200 msec	
QRS duration	<70 or >110 msec	
QTc interval[2] (Fridericia's)	>450 msec	>470 msec

1. A heart rate from 100 to 110 beats per minute (bpm) can be rechecked by ECG or vitals within 30 minutes to verify eligibility.
2. The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in 208132 will be Fridericia's formula.

25. Any significant arrhythmia or ECG finding (eg prior myocardial infarction, sinoatrial pauses, bundle branch block, or conduction abnormality) which, in the opinion of the Investigator OR ViiV Medical Monitor, will interfere with the safety for the individual participant.

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

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories with at least 120 calories from fat), completed within approximately 30 minutes just prior to dosing. Prior to the two serial intensive blood PK collection days, to be done on Clinic Visit 1 and on Clinic Visit 5, participants will be required to fast for at least 8 hours [overnight] prior to the morning check-in.

- Refrain from excessive consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 3 days prior to the first dose of study medication until the day after the final dose. Excessive consumption is defined as more than one glass of wine or juice or one fruit per day, in combination.

6.3.2 Alcohol, Tobacco and Marijuana

- During the study alcohol consumption will be limited to the following: An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.

No alcohol will be consumed on the in-clinic Intensive PK days (Clinic Visit 1 and Clinic Visit 5), until after the final assessment of the day and release from the clinic.

- Only clinically minor to moderate use (as determined by the PI/SI) of tobacco products will be allowed during trial participation, with extremely limited use on the in-clinic Intensive PK days (Clinic Visit 1 and Clinic Visit 5).
- Subjects should refrain from the use of marijuana during the treatment period.

6.3.3 Activity

Participants should abstain from strenuous exercise during the treatment period.

6.3.4 Counsel regarding Safe Sex Practices

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

6.4. Screen Failures

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

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

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK3640254 Mesylate Salt	Placebo to match GSK3640254 Mesylate Salt
Dosage formulation:	capsule	capsule
Unit dose strength(s)/Dosage level(s):	5mg, 20mg, and 100mg	placebo
Route of Administration	oral	oral
Dosing instructions:	Each dose of study treatment will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories with at least 120 calories from fat).	Each dose of study treatment will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories with at least 120 calories from fat).
Packaging and Labeling	Blinded Study Treatment will be provided in high-density polyethylene (HDPE) bottles. Each bottle will be labelled as required per country requirement.	Blinded Study Treatment will be provided in HDPE bottles. Each bottle will be labelled as required per country requirement.
Manufacturer	Shanghai STA Pharmaceutical Product Co. Ltd (previously named as Wuxi AppTec (Shanghai) Co. Ltd)	Shanghai STA Pharmaceutical Product Co. Ltd (previously named as Wuxi AppTec (Shanghai) Co. Ltd)

7.2. Dose Modification

Dose modifications, as assigned in each cohort, will not be made.

7.3. Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

Study treatments will be dispensed at the study visits indicated in the SOA.

Returned study treatment should not be redispensed to another participant.

7.4. Blinding and Interim Analysis

This will be a double-blind study with participants and site staff blinded. The sponsor will be unblinded (meaning those staff may have access to unblinded data). This early phase study of relatively small size will not contain an external Data Monitoring Committee (DMC). The ongoing monitoring and informal interim analysis will be overseen by an experienced central VH/GSK study team. For the informal interim analysis, the VH/GSK study team including physicians, statistician, programmer, study leads, virologist and clinical pharmacokinetic staff will have access to unblinded data and present data in a blinded fashion when interacting with site staff. Other VH/GSK staff will remain blinded unless unblinding becomes necessary.

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

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

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

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from VH or GSK.

7.6. Treatment Compliance

- When participants are dosed at the site, they will receive study treatment 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 treatment 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 treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

- If participants self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed preferably through a visual technology such as Skype, FaceTime, WhatsApp or the like, if at all possible and locally permitted. At a minimum, a phone call should be made to each participant daily, through querying the participant during the site visits and documented in the source documents and CRF. If the decision is made to utilize a diary cards in this study, a record of the number of study treatment capsules dispensed to and taken by each participant via "patient diary" must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

7.7. Concomitant Therapy

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

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Acetaminophen/paracetamol at doses of ≤2 grams/day or nonsteroidal anti-inflammatory drugs (NSAIDs) are permitted for use any time during the study and their use documented in the CRF. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Participants must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the counter because of the potential for interactions between such treatments and the study medications. Concomitant medications that may significantly interact with GSK3640254 as a perpetrator or a victim such as a strong CYP3A inhibitor (Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole etc), strong CYP3A inducer (e.g. phenobarbital, dexamethasone, carbamazepine, phenytoin, rifampin, rifabutine, St John's wort, etc), or substrate of OATP1B3 (e.g. telmisartan, valsartan, olmesartan, rifampin, statins such as atorvastatin, rosuvastatin, pitavastatin) are not permitted.

7.8. Treatment and Care after the End of the Study

Given the lack of longer term clinical benefit (Section 3.3.2), VH recognizes the balance between the need to conduct an early phase monotherapy clinical trial (for the larger and long term unmet medical need) and the need for HIV-1 infected treatment naïve patients to receive cART as soon as possible after diagnosis. To meet both needs, this trial design is efficient in screening (shortest period: 14 days) and treatment/follow-up (shortest period: 18 days in study Part 1 and 10 days in study Part 2). A clinical trial commitment of as short as ~1 month is expected. After this time, VH expects all participating patients to receive local standard of care cART.

VH recognizes some HIV-1 infected adults may encounter barriers to accessing cART. Where it has been determined by the Investigator to be an acceptable option, participants receiving study treatment will have the option (but are not required) to receive reimbursement from the Sponsor for locally marketed ARVs (after the completion of dosing and through the study final follow-up visit) for up to a maximum of 90 days. The selection of ARVs will be investigator-chosen based upon local standard of care.

The investigator is responsible for ensuring that participants will be referred for prompt cART initiation after completion of the study, whether or not VH is providing reimbursement for post-study treatment.

In the case of Part 2, participants will start Investigator selected, prescribed and provided cART immediately after the completion of the primary endpoint; i.e., specifically to be administered in the clinic on Day 8 after the blood collection has been performed.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

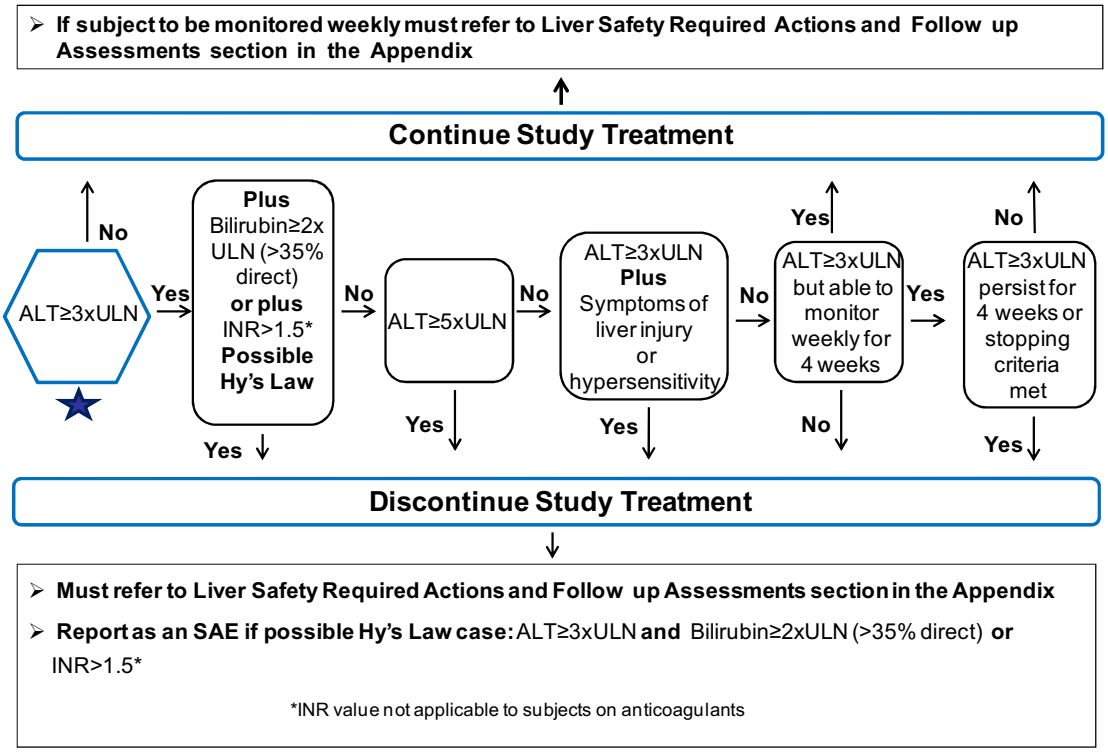
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

These protocol guidelines are in alignment with the Food and Drug Administration (FDA) premarketing clinical liver safety guidance.

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

Discontinuation of study treatment for abnormal liver tests is required when a participant meets one of the conditions outlined in the algorithm:

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7 in Section 12.7.

8.1.2. QTc Stopping Criteria

- The *same* QTcF correction formula *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 electrocardiograms obtained over a brief 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 subject will be withdrawn from the study.

Finally, this subject should have repeated unscheduled ECGs until their QTcF measurement returns to their original averaged QTcF value at Day 1 pre-dose.

See the **SOA** for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Individual Participant Laboratory Abnormality and AE 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 treatment should be stopped.

- Any clinically significant AE deemed to require discontinuation of investigational product
- Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement
- Any Grade 3 or higher allergic reaction
- Any Grade 3 or higher Psychiatric AE
- New onset suicidal ideation
- Any Grade 3 or higher AE related to study medication.
- Any Grade 4 AE or laboratory abnormalities (with the exception of an asymptomatic grade 4 cholesterol, triglyceride or CPK increase)

8.1.4. Temporary Discontinuation

Withdrawal of study treatment requires withdrawal from the study. See Section 8.2.

8.1.5. Rechallenge

8.1.5.1. Study Treatment Restart or Rechallenge

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

8.2. 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.

- A participant who is withdrawn from the study for any reason related to safety (listed in Section 8.1.3 or otherwise) will be continued to be followed to assess the outcome of the safety event that triggered discontinuation of study drug.

- 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.

- Refer to the SOA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- Termination of the study by VH. Safety data will be reviewed by the Sponsor in-stream by single case and collectively. If a safety concerns arises, a decision about continuation of the study will be made.
- Loss of ability to freely provide consent due to treatment of either a psychiatric or physical (eg, infectious disease) will require withdrawal
- Repeat non-adherence by the participant with the requirements of the protocol or treatment (as determined by Investigator in consultation with the Medical Monitor) will require withdrawal.

If a participant withdraws from the study, he/she should complete a follow-up visit 7-14 days after treatment was stopped (conducted as a Visit 9) in study Part 1, and 3-5 days after treatment was stopped (conducted as a Visit 7) in study Part 2. If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the subject for assessment of adverse events.

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- In-clinic assessments should occur in the following order, prior to administration of study treatment, and should be conducted so as to allow the blood draw to occur as close as possible to the nominal time:
    1. 12-lead ECG

2. vital signs

3. blood draws

- Study procedures and their timing are summarized in the SoA
- 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 treatment.
- Adherence to the study design requirements, including those specified in the SOA (Section 2), 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 (eg, blood count) and obtained before signing of informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe 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.

9.1. Efficacy Assessments

9.1.1. HIV-1 RNA Sampling

Plasma for quantitative HIV-1 RNA will be generated at timepoints listed in the SOA (Section 2).

An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 40 copies/mL will be used.

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

9.1.2. Lymphocyte Subsets by Flow Cytometry

Blood samples will be obtained from each participant for the analysis of lymphocyte subsets by flow cytometry at the timepoints listed in the SOA (Section 2).

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

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4. As described in Appendix 4, intensity of AEs (and lab abnormalities) will be graded using the division of AIDS (DAIDS) Grading table.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

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

- All SAEs will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SOA (Section 2).
- All AEs will be collected from the start of treatment until the final follow-up visit at the time points specified in the SOA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (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 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

Appropriate questions to ask include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

- "Have you experienced any alteration in personality, behavior, mood or any altered mental status?"

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 12.4) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 (Section 12.4) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

9.2.6. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of the pregnancy (delivery or termination).

- 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 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of the assigned study treatment greater than the assigned dose within a 30-hour time period will be considered an overdose.

VH/GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose, the investigator should:

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SOA (Section 2).

9.4.1. Physical Examinations

- A physical exam will include, at a minimum, assessments of the skin, heart, lungs, and abdomen (liver and spleen)
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Pulse rate, respiratory rate, and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed 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 (eg, television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include, systolic and diastolic blood pressure, and pulse and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

9.4.3. Electrocardiograms

- Triplicate and Single 12-lead ECG will be obtained as outlined in the SOA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SOA 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 2 days after the last dose of study treatment 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.
- Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

- All study-required laboratory assessments will be performed by a central laboratory.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered in the CRF.

9.4.5. Suicidal Risk Monitoring and Management of Emergent Psychiatric Symptoms

GSK3640254 is not a CNS 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 patient will discontinue from the trial and the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

As described in Section 8.1.3, new onset suicidal ideation at any time will result in immediate discontinuation from the trial and the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. 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 PI/SI. Any pharmacotherapy should be discussed with the medical monitor.

- Any Grade 3 or 4 Psychiatric AE: As described in Section 8.1.3, 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).

9.4.6. GI Toxicity Evaluation and Monitoring Plan

Pre-clinical 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 gastrointestinal symptoms (Table 3). The Investigator may contact the VH Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the trial.

Table 3 GI 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 trial.**
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 trial are available elsewhere (Rome Foundation, 2014).
PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history (Hasler, 2012). Acutely, the investigator may assess for signs of intravascular volume depletion (eg, orthostasis) and/or aspiration of vomitus as appropriate. Abdominal tenderness and guarding may indicate inflammation. The presence of fecal blood can indicate mucosal damage (eg, 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 (eg, 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[a]	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 (PCR) for viruses (eg, Cytomegalovirus [CMV]) For participants who are infected with H. pylori discontinuation from the trial is necessary. Management should be targeted at addressing the underlying pathology.
Grade 3 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • CT scan to identify gastrointestinal inflammation • Upper endoscopy with biopsy as indicated (eg, mucosal injury or the presence of red flags). Management should be targeted at addressing the underlying pathology.

Grade 4 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 and Grade 3 • An acute abdominal series Initial management can include correction of hemodynamic and electrolyte abnormalities as clinically indicated. After stabilization, management should be targeted at addressing the underlying pathology.

a. 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.

9.5. Pharmacokinetics

- Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the SOA. A maximum of 5 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 (as well as each subsequent dose) will be recorded.

- Samples will be used to evaluate the PK of GSK3640254. Each plasma sample will be divided into aliquots as outlined in the laboratory manual. Samples collected for analyses of GSK3640254 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

- Once the plasma has been analysed for GSK3640254, any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate protocol.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Intensive PK sampling (Clinic Visit 1 and Clinic Visit 5) begins with a morning pre-dose sampling, i.e, prior to the administration of the morning dose of the study treatment on the day of the visit. The pre-dose sampling should be done approximately 24 hours after the morning doses of the study drugs were taken the day prior to the visit. This pre-dose blood sampling will include the collection of the other parameters as well.

The subsequent 8 time points include samplings through Hour 12, with a final sample collected at Hour 24. The subject will either stay overnight or will return to the clinic so that the final sample can be collected at Hour 24.

It is critical to capture the exact date and time of each PK sample collection, even if drawn slightly off-schedule. If a sample collection time point is missed/late/not done within the specified window and the next collection time point has not yet been reached, collect the missed time point, and record the exact time of that collection, then get back on track for the next time point/on-time collection.

Table 4 below lists the sampling schedule to be followed for the assessment of intensive pharmacokinetics. Further details of PK blood collection and sample processing will be provided in the central clinical laboratory manual.

Table 4 Intensive Pharmacokinetic Sampling Schedule and Other Activities at Clinic Visit 1 and Clinic Visit 5

	Time (Event)	Window for blood draw	Time (Relative to Dosing) Hour: Min
Clinic Visit 1 And Clinic Visit 5	morning pre-dose work: ECGs, vitals and full blood draw to include the pre-dose PK collection		
	Eat Meal. Administer study treatment and start the clock for subsequent blood draws.		00:00
	1 hr PK blood draw	± 5 minutes	01:00
	2 hr ECG and PK blood draw	± 15 minutes	02:00
	3 hr PK blood draw	± 15 minutes	03:00
	4 hr ECG and PK blood draw	± 15 minutes	04:00
	5 hr PK blood draw	± 15 minutes	05:00
	6 hr ECG and PK blood draw	± 15 minutes	06:00
	8 hr PK blood draw	± 30 minutes	08:00
	12 hr PK blood draw	± 2 hours	12:00
Next Day	24 hr (morning pre-dose) PK blood draw[1, 2]	± 2 hours	24:00
	Eat Meal and administer study treatment.		

1. This 24-hr pre-dose PK blood draw will be done at the same time as the collection for the lab kit on the next day.
2. In study Part 1, if the Visit 5 Intensive PK visit is done on Day 10, this 24-hr PK blood draw will be done at the same time as the collection for the lab kit on Day 11. Otherwise, this 24-hr blood draw is the only draw done on Day 9 (if the clinic visit is done on Day 8) or Day 10 (if the clinic visit is done on Day 9).

9.6. Pharmacodynamics

See Section 10.3.3.

9.7. Genetics

Genetics are evaluated in this study.

A 6 mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected on Day 1 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 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual and the SRM.

9.8. Biomarkers

Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide plasma for viral genotype and phenotype analysis, at the times listed in the SOA (Section 2). Details concerning the handling, labeling and shipping of these samples will be supplied separately.

Genotypic and phenotypic analyses will be carried out by using Gag/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the Gag/PR region will include susceptibility to GSK3640254. Analysis will be done on samples collected in study Part 1 on Day 1 and Day 11 initially, and on samples collected in study Part 2 on Day 1 and Day 8 initially, with other timepoints analyzed as data emerge for viral load response.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

10.1.1. Sample Size Considerations

The primary objectives of this study are to investigate the safety, tolerability and antiviral activity of GSK3640254 over a 10-day treatment period in study Part 1 and over a 7-day treatment period in study Part 2. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study.

The sample size for this study is based primarily on feasibility to provide adequate precision for the estimations.

Based on data from the short-term monotherapy study of BMS-955176/GSK3532795 POC (AI468002) study and GSK2838232 POC study**,** we assumed the maximum change from baseline viral load drop (VLD) values on log scale for individual participants from the higher dose in Part 1 follow a normal distribution. Therefore, we conducted 1000 trial

simulations in Fixed and Adaptive Clinical Trial Simulation (*FACTS*) software using the normal distribution with mean of change from baseline VLD on log scale at 0.5 to 2 copies, SD=0.4, and sample sizes=6 for Part 1 higher dose.

Using Bayesian calculation with non-informative priors for the mean and weakly informative priors for the error parameters, Normal (0, 100) for mean and Inverse Gamma (0.35, 0.0875) for error parameters, the posterior probability to achieve a clinically relevant cut-point of 1.3 log was calculated for each simulated trial, and percentage of the trials with posterior probability of mean viral load drop (VLD) at the higher dose in Part 1 >1.3 log (given the true mean VLD on log scale) ≥20% was calculated and are shown below in Table 5.

Table 5 Percentage of the trials with posterior probability>=20% for Part 1 higher dose using sample size=6

True Mean VLD on log scale	Posterior Probability ≥20%	Posterior Probability <20%
0.5	0.0%	100.0%
0.7	0.1%	99.9%
0.8	0.6%	99.4%
0.9	4.6%	95.4%
1	15.0%	85.0%
1.1	35.9%	64.1%
1.2	60.8%	39.2%
1.3	81.8%	18.2%
1.4	92.4%	7.6%
1.5	97.9%	2.1%
1.6	99.8%	0.2%
1.7	100.0%	0.0%
2	100.0%	0.0%

The precision of the dose response curve (with sample size N=6) is provided in Table 1 (Section 5.5.1).

10.1.2. Sample Size Sensitivity

Similar simulations in FACTS were conducted using sample sizes of 8 for Part 1 higher dose. Using Bayesian calculation, the posterior probability to achieve a cut-point 1.3 log was calculated for each simulated trial, and percentage of the trials with posterior probability greater than or equal to 20% was calculated (given the true mean VLD on log scale) and are shown below in Table 6.

Table 6 Percentage of the trials with posterior probability ≥20% for Part 1 higher dose using sample size=8

True Mean VLD on log scale	Posterior Probability ≥20%	Posterior Probability <20%
0.5	0.0%	100.0%
0.7	0.0%	100.0%
0.8	0.6%	99.4%
0.9	2.5%	97.5%
1	10.2%	89.8%
1.1	27.4%	72.6%
1.2	56.2%	43.8%
1.3	81.3%	18.7%
1.4	93.8%	6.2%
1.5	98.9%	1.1%
1.6	99.8%	0.2%
1.7	100.0%	0.0%
2	100.0%	0.0%

Compared with the results of sample size=6 in Table 5, we only found slightly difference for the operation characteristics. It would be sufficient using sample size=6 for the interim analysis Go/No Go decision making.

10.1.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

10.2. Populations for Analyses

Intent to Treat Exposed Population (ITT)
The ITT-Exposed Population is defined as all participants who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. This will be the primary population for the final efficacy analysis for all active treatment groups.

Per Protocol Population (PP)
The Per Protocol Population is defined as all participants who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of major protocol deviation.

Safety Population
The Safety Population is defined as all participants who are enrolled into the study with documented evidence of having received at least 1 dose of randomized treatment.

Pharmacokinetic Population
The PK Population will include all participants who receive GSK3640254 and undergo plasma PK sampling during the study. Participants for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK3640254

concentration-time data. Results from samples collected from a participant with emesis occurring within 2 hours of the dose will not be considered as evaluable.

10.3. Statistical Analyses

10.3.1. Interim Analysis

An informal unblinded interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after participants of Part 1 complete their Day 12 visit. If the review of Part 1 highest dose shows that exposures are similar or higher than observed with 200 mg QD in healthy participants, this dose will be the highest dose in this study and only in this case, the Bayesian posterior probability (based on Part 1 higher dose data) that the log10 mean VLD from baseline is greater than a cut-point=1.3 log will be calculated for the Go/No Go decision for Part 2:

- If the probability is less than 20%, the trial will not move forward into Part 2 (No Go decision).
- Otherwise, the study team will review the whole Part 1 data in order to make a dose selection decision for the subsequent Part 2 cohorts

The study team will review the safety, tolerability, PK and antiviral activity data in order to confirm the dose selection for Part 2 cohorts. If the exposure to GSK3640254 200mg (Part 1 higher dose) looks similar or higher to those obtained with 200 mg QD in healthy volunteers in prior studies, and the effect observed at the Part 1 low dose is as anticipated, the Part 2 doses will be as initially planned as described in Section 5.5.2. If the exposure to GSK3640254 200mg are significantly lower than what anticipated (e.g. lower by at least 25%), the new highest dose predicted to provide a 200 mg equivalent exposure will be estimated and proposed for Part 2. The team will evaluate and possibly run the same Bayesian criteria to test the projected new highest dose VL drop in the interim analysis. If the effect observed with the Part 1 low dose is not as anticipated, the PK/PD model may be refined, and the Part 2 target effects and doses may be updated.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by visit. The analyses will be done for both PP and ITT exposed population if two populations are not the same.

10.3.2. Primary Analyses

The final analysis will be performed after the completion of the study and final datasets authorization. Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by participant, period, day, and time, noting treatment; summaries will be presented by treatment, visit/day, and time. Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and %CVb for continuous variables, whereas n and percent will be used as summary statistics for categorical variables. Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only

the scheduled assessments will be included in the summary tables. Version 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the Reporting and Analysis Plan (RAP).

10.3.2.1. Safety Analyses

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

10.3.2.2. Efficacy Analyses

Both the PP and ITT Populations will be used for all efficacy analyses if there are dropouts. Plasma HIV-1 RNA max change and change from baseline during the study will be calculated for each participant and on each assessment visit/day.

Plasma HIV-1 RNA will be listed by treatment, participant, and assessment visit/day and summarized by treatment and assessment visit along with change from baseline.

Plots of mean and median plasma HIV-1 RNA actual and change from baseline data will be generated by treatment and assessment visit.

- Plasma HIV-1 RNA change from baseline to the nadir (maximum change from baseline) will be calculated for each participant and summarized by treatment.

Together, the data from Parts 1 and 2 will investigate the complete dose-exposure-response curve and the impact of lower doses/exposures on potential development of resistance.

10.3.2.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GSK. Plasma GSK3640254 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit:

Plasma GSK3640254 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	area under the plasma concentration time curve from zero to 24 AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag)
PART 1: Day 9±1	AUC(0-τ), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), half-life (t1/2), apparent oral clearance (CL/F).

and PART 2: Day 7	

Results based on samples collected from a participant with emesis within 6 hours of dosing will not be considered as evaluable.

All PK data will be stored in the R&D archives, GSK.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK3640254 PK parameters, with the exception of Tmax and Tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK3640254 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 9±1 in study Part 1 and Day 7 in study Part 2 [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using statistical analysis software (SAS) Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI.

The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 9±1 with Day 1 PK for each dose in Part 1 and comparisons of Day 7 with Day 1 PK for each dose in Part 2 will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Visit 4 and 6 will be used for steady-state assessment.

10.3.3. Secondary Analyses

10.3.3.1. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various PK parameters (e.g., AUC, Cmax, Cτ, etc.) and PD measures (e.g., maximum log10 reduction from baseline in plasma HIV-1 RNA or safety parameters) will be explored using various models including Emax. The relationship between dose and PD measures will also be explored.

Details of the PK/PD exploratory analyses will be provided in the RAP.

10.3.3.2. Viral Genotyping and Phenotyping Analyses

Viral genotypic/phenotypic data will be listed and descriptive summaries will be provided. Details of the analyses will be provided in the clinical virology report.

11. REFERENCES

Bristol-Myers Squibb Document Number 930109388, 1.0; BMS-TMF-3548385 1.0. Clinical Study Report: A Randomized, Double-Blind, Double-Dummy, Positive-Controlled, Crossover Study to Determine Electrocardiographic Effects of BMS-955176 in Healthy Subjects, 13-JAN-2017

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

GSK Document Number 2016N302783_00. Clinical Study Report: A Phase 2b Randomized, Active-Controlled, Double-Blind Trial to Investigate Safety, Efficacy and Dose-response of BMS-955176/GSK3532795, Given on a Backbone of Tenofovir/Emtricitabine, in Treatment-Naive HIV-1 Infected Adults – Week 24 Interim Analysis, 21-JUN-2017

GSK Document Number 2018N375454_00. Clinical Pharmacology Synopsis. A single centre, 2-period, randomized, open-label Phase 1 study to assess the relative bioavailability of a mesylate salt capsule of GSK3640254 compared to a hydrochloride salt capsule in healthy participants. September 2018.

GSK Document Number 2018N375461_00. Clinical Pharmacology Synopsis. A Double-Blind (Sponsor Unblinded), Randomized, Placebo- Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3640254 in Healthy Participants. September 2018.

GSK Document Number 2018N379610_00. Clinical Investigator's Brochure for GSK3640254, September 2018

Hasler WL Nausea, Vomiting, and Indigestion: Introduction. Chapter 39. Harrisons Principles of Internal Medicine 18th edition. 2012. McGraw Hill

International Antiviral Society (IAS)–USA ART Treatment of Adult HIV Infection: 2015 Recommendations of the International Antiviral Society-USA Panel. Wensing AM et al. 2015 update of the drug resistance mutations in HIV-1. Topics in Antiviral Medicine October/November 2015: 23(4). Available at: http://www.iasusa.org/sites/default/files/tam/23-4-132.pdf.

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

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035–1043.

Rome Foundation. Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. Available: http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf. Accessed Dec 22 2014.

Soll AH and Graham DY. Peptic Ulcer Disease. Chapter 40. Textbook of Gastroenterology. 5th edition. 2009. Blackwell Publishing.

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017].

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ART	Anti-retroviral therapy
ARV	Anti-retroviral
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
AUC(0-24)	Area under the plasma concentration time curve from zero to 24
β-HCG	Human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BMS	Bristol-Myers Squibb
cART	Combination anti-retroviral therapy
C0	Concentration, pre-dose
C24	Concentration, 24 hours post-dose
CAp24	Capsid protein 24
CD4	Cluster of designation 4
CD8	Cluster of designation 8
CDC	Center for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CIB	Clinical Investigator's Brochure

CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent oral clearance
CMV	Cytomegalovirus
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
Ct	Concentration at end of dosing interval
CV	Cardiovascular
CVb	Between-participant coefficient of variation
DAIDS	Division of AIDS
DNA	Deoxyribonucleic acid
EC90	Effective concentration
ECG	Electrocardiogram
Emax	Effect, at the maximum
EMEA	European Medicines Agency
FACTS	Fixed and Adaptive Clinical Trial Simulation
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First-time-in-human
Gag	Group-specific antigen

GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C antibody
HDPE	High-density polyethylene
HDL	High density lipoprotein
HIV-1	Human immunodeficiency virus-1
HRT	Hormonal replacement therapy
ICF	Informed consent form
IEC	Independent Ethics Committee
INR	International normalized ration
IQ	Inhibitory quotient
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IVRS/IWRS	Interactive Voice/Web Response System
LDL	Low density lipoprotein

LOAEL	Lowest observed adverse effect level
LLOD	Lower limit of detection
MAD	Multiple ascending dose
MedRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Maturation inhibitors
MOA	Mechanisms of action
MSDS	Material Safety Data Sheet
msec	Milliseconds
NOAEL	No-observed-adverse-effect-level
NSAIDS	Nonsteroidal anti-inflammatory drugs
PBAEC90	Protein binding adjusted concentration
PBO	Placebo
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
POC	Proof of Concept
PGX	Pharmacogenetics
PP	Per protocol
PPL	Physician Product Lead
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula

R	Accumulation ratio
RAP	Reporting and Analysis Plan
RBC	Red blood cells
REML	Restricted Maximum Likelihood
RNA	Ribonucleic Acid
SAD	Single ascending dose
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SI	Sub-Investigator
SOA	Schedule of activities
SOC	System Organ Class
SP1	Spacer peptide 1
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
tlag	Absorption lag time
tmax	Time of occurrence of Cmax
TN	Treatment naïve
ULN	Upper limit of normal
VH	ViiV Healthcare

VLD	Viral load drop
WBC	White blood cells
WoCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by ViiV Healthcare
DAIDS
FaceTime
MedDRA
Phoenix
SAS
SKYPE
WhatsApp
WonNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-Required Safety Laboratory Assessments

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

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (if needed to determine women of non-childbearing potential) • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed)[2] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody [HCVAb], with reflex to HCV RNA if positive). • PCR (HIV-1 diagnostic PCR) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • All study-required laboratory assessments will be performed by a central laboratory The results of each test may be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (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.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded or the participant has undergone emergency unblinding.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

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.

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.

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.

Committees Structure

The Safety Review Team (SRT) is a VH/GSK cross-functional team reviewing all available safety data related to the project, including in-stream data from this study, in an ongoing manner. The SRT is an internal VH/GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety.

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.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV Healthcare site or other mutually-agreeable location.
- ViiV Healthcare 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.
- ViiV Healthcare will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with ViiV Healthcare Policy.

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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently

approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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 Study Reference Manual (SRM).

Study and Site Closure

ViiV Healthcare or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of ViiV Healthcare. 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 treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

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 (eg, 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.

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 (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's

medical records to VH/GSK in lieu of completion of the VH/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 & functional activities
- Severe: inability to perform usual social & 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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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.

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 eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be

taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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 at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Pregnancy Testing

Women of Childbearing Potential are excluded from trial participation.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to VH/GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be

forwarded to VH/GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to VH/GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

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

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** International normalized ratio (INR)>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to VH/GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and VH/GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, within 5 days after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** 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)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

12.8. Appendix 8: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the hyperlink here to the DAIDS Grading Table.

Alternatively, paste this into your browser: https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf

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

The PI/SI may contact the VH Medical Monitor with questions on estimating the severity grade for parameters not identified in the original table.

All deaths related to an AE are to be classified as **Grade 5.**

12.9. Appendix 9: CDC Classification for HIV-1 Infection (2014)

- Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.

- **HIV infection, stage 0**

- Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

- **HIV infection, stage 1**

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and

  - CD4+ T-lymphocyte count of ≥500 cells/μL, or

  - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

- **HIV infection, stage 2**

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and

  - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or

  - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

- **HIV infection, stage 3 (AIDS)**

- Laboratory confirmation of HIV infection, and

  - CD4+ T-lymphocyte count of <200 cells/μL, or

  - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or

  - Documentation of an AIDS-defining condition (see below).

- Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

- **HIV infection, stage unknown**

- Laboratory confirmation of HIV infection, and

  - No information on CD4+ T-lymphocyte count or percentage, and

  - No information on presence of AIDS-defining conditions.

- **Stage-3-defining opportunistic illnesses in HIV infection**

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary

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

12.10. Appendix 10: Protocol Amendment History

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

Amendment 1 (28-Sep-2018)

Overall Rationale for the Amendment: The original version of the protocol was not submitted to any health authority (HA) worldwide. Key elements of the original protocol design were discussed with the United States Food and Drug Administration (US FDA) in the context of pre-Investigational New Drug (IND) feedback (i.e. scientific advice). To this end, the overall design, duration, and sample population remain the same. However, minor changes were made to exclusion criteria, patient monitoring, and reasons for discontinuation to enhance the safety of trial participants. Finally, other administrative changes and updates were made (e.g. succinct results from two Phase 1 clinical trials in healthy volunteers).

Section # and Name	Description of Change	Brief Rationale
Section 1, Synopsis, Rationale	Updated text to reflect the most current information regarding the first-time-in-human (FTIH) 207187 study.	Updated information is now available.
Section 1, Synopsis, Overall Design	Provided a justification for the use of placebo in the study.	For completeness.
Section 1, Synopsis, Treatment Groups and Duration	Inserted the caveat of local permissibility to the suggestion that observed dosing may be achieved via various forms of video calling technology.	Acknowledging there may be cases where this method may not be locally allowed.
Section 2.2, Part 1 and Part 2 Treatment, Post-Dosing and Follow-up Periods	Redesigned the format of the entire table.	For clarity regarding procedures to be done at the in-clinic visits versus the visits done via video/phone.
	To footnote 3: Inserted the caveat of local permissibility for the suggestion that observed dosing may be achieved via various forms of video calling.	Acknowledging there may be cases where this method may not be locally allowed.
	Inserted new footnotes 7 and 9	For clarity regarding the pharmacokinetic (PK) visit relative to visit optionality.
	Regarding Single, Pre-dose PK and Intensive PK (and new footnote 7): Removed the collection need for single, pre-dose PK sample on Day 2, and added a footnote of consideration for collection the single, pre-dose PK samples on Day 11.	Removed redundancy, as the Day 1, 24-hr PK sample is the same as the Day 2, single, pre-dose collection. This could hold true as well for the Day 11 single, pre-dose PK collection if the Intensive PK event occurs on Day 10.
Section 3.2, Background	Updated reference information with the most current document identification	Updated information is now available.
Section 3.2.2, Preliminary Safety and PK Data in Study 207187	Preliminary Safety and PK Data in Study 207187 updated/added	Updated information is now available.

Section # and Name	Description of Change	Brief Rationale
Section 3.2.3, Preliminary Safety and PK Data in Study 208131	Preliminary Safety and PK Data in Study 208131 updated/added	Updated information is now available.
Section 3.3, Benefit/Risk Assessment	Minor text adjustments, and updated information for reference documents	Updated information is now available.
Section 3.3.1, Risk Assessment	Cardiovascular category: Added information about new corrected QT (QTc) Stopping criteria	Strengthened conservative measures for patient safety.
	Gastrointestinal intolerability and toxicity category: Added text directing the reader to the Investigator's Brochure (IB) for summaries of rates of gastrointestinal (GI) adverse events (AEs), and other minor text adjustments.	Current information from the FTIH 207187 and RBA 208131 studies is available.
	Neurologic/psychiatric safety category: Added text directing the reader to the IB for summaries of rates of Neurologic and Psychiatric AEs, and other minor text adjustments	Current information from the FTIH 207187 and RBA 208131 studies is available, and referred to new guidance for the management of emergent psychiatric symptoms.
	Human immunodeficiency virus (HIV) Resistance to GSK3640254 category: provided information to indicate there is no cross-class resistance.	Provided information to indicate participation in this trial will not interfere with the selection of a combination antiretroviral therapy (cART) regimen at the completion of the study.
Section 3.3.3, Overall Benefit:Risk Conclusion	Outdated information for study 207187 was removed.	Updated information is now available.
Section 5.1, Overall Design	Expanded the existing justification for the use of placebo in Part 1 and in Part 2	Clarity.
Section 5.1.1.2, Treatment Phase	Inserted the caveat of local permissibility for the suggestion	Acknowledging there may be cases where this method may not be locally

Section # and Name	Description of Change	Brief Rationale
and Follow-up Period, Treatment Phase Day 1 – Day 10	that observed dosing may be achieved via various forms of video calling.	allowed.
Section 5.1.1.2, Treatment Phase and Follow-up Period, Follow-up Visits Day 11-17 and Final Follow-up Visit Day 18-24	Text modifications regarding the start of medications in the post-dosing period.	Clarification/Correction.
Section 5.4, Scientific Rationale for Study Design	Preliminary Safety and PK Data in Study 207187 updated/added, and other minor text adjustments.	Updated information is now available.
Section 6.2, Exclusion Criteria, #8	Extended exclusion criterion for laboratory abnormalities from just Grade 4 to Grade 2-4, and included lipid abnormalities as exceptions.	Strengthened conservative measures for patient safety.
Section 6.2, Exclusion Criteria, #24	Reduced the exclusionary values for both PR interval and QRS duration.	Strengthened conservative measures for patient safety.
Section 7.1, Treatment Administration	Added descriptive information for the placebo	Clarity needed to ensure it is understood that the placebo will look exactly like any one of the active dose capsules of GSK3650254
	Changed manufacturer from Wuxi to Shanghai STA Pharmaceutical Product Co.	STA is a subsidiary of Wuxi, and is the location to where the manufacture has been transferred.
Section 7.4, Blinding	Modified the title due to the addition of text explaining the role of the study team in the interim analysis in lieu of the inclusion of a data monitoring committee (DMC).	For clarity.
Section 7.6,	Inserted the caveat of local	Acknowledging there may be cases

Section # and Name	Description of Change	Brief Rationale
Treatment Compliance	permissibility for the suggestion that observed dosing may be achieved via various forms of video calling.	where this method may not be locally allowed.
Section 7.8, Treatment and Care after the End of the Study	More formally describe the post dosing treatment expectations/goals for participants	For clarity.
Section 8.1.2, QTc Stopping Criteria	Added new QTc Stopping Criteria	Strengthened conservative measures for patient safety.
Section 8.1.3, Individual Participant Laboratory Abnormality and AE Stopping Criteria	Added new stopping criteria for psychiatric AEs, and for related AEs.	Strengthened conservative measures for patient safety.
Section 9.4.5, Suicidal Risk Monitoring	Added new guidance for the management of emergent suicidal and non-suicidal psychiatric AEs.	Strengthened conservative measures for patient safety.
Section 9.4.6, GI Toxicity Evaluation and Management, Footnote *a* to the table	Adjusted the grading and relatedness of GI AEs that will now require discontinuation and not just a consideration of discontinuation.	Strengthened conservative measures for patient safety.
Section 9.5, Pharmacokinetics	Removed the 0 hr, 00:00 references in the text associated with the pre-dose blood sampling and attached those to the actual dosing time.	Clarification/Correction
Section 9.5, Pharmacokinetics, Table 4	Removed the 0 hr, 00:00 references in the table associated with the pre-dose blood sampling and attached those to the actual dosing time. Added footnotes regarding the 24-hr PK blood draw to be consistent with new	Clarification/Correction

Section # and Name	Description of Change	Brief Rationale
	footnotes in Section 2.2.	
Section 9.7, Genetics	Changed the genetics blood sampling volume from 10 mL to 6 mL	Correction.
Section 11, References	Updated with the most current documents available and that were used to amend portions of this protocol.	Updated information is now available.
Throughout	Minor editorial and document formatting revisions	Minor, therefore not summarized

Amendment 2 10-JAN-2019

Overall Rationale for the Amendment: Feedback from a Health Authority has provided greater specificity and clarification to existing exclusion criteria on psychiatric disease. Additionally, we have clarified that patients who are recently infected with HIV-1 should be excluded. Next, the human PK data available from Study 207187 (SAD/MAD) resulted in the removal of contraceptive requirements of male participants and any pregnancy monitoring requirements of female partners (of male participants). Further clarification on prohibited concomitant medications was provided. Finally, minor changes/clarifications were made to patient monitoring and reasons for discontinuation.

Individually and in combination, all of these changes will not have a significant impact on the safety of clinical trial participants.

Section # and Name	Description of Change	Brief Rationale
Section 2.2, Part 1 and Part 2 Treatment, Post-Dosing and Follow-up Periods	Corrected some ECG collections during the post-dosing phase to indicate those that are not done as a pre-dose sampling	Correction
Section 2.2, Part 1 and Part 2 Treatment, Post-Dosing and Follow-up Periods Section 9.5, Table 4 footnote #2	Corrected some PK samples collections during the post-dosing phase to indicate those that are not done as a pre-dose sampling	For clarity
Section 6.1, Inclusion Criteria, #7 Section 9.2.6, Pregnancy Section 12.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information	Removed contraceptive requirements and any pregnancy reporting requirements for female partners of male participants.	Preclinical data shows that GSK3640254 is not genotoxic, and though the teratogenicity is unknown, data suggests toxicity to sperm or embryo at therapeutic levels unlikely. Thus, there is no impact on the risk/benefit assessment.
Section 6.2, Exclusion Criteria	Added additional exclusion criterion on patients with recent HIV-1 infection.	This exclusion criterion provides further clarification on excluding patients with recent HIV-1 infection who are not appropriate for participation in a clinical trial.
Section 6.2, Exclusion Criteria	Added greater specificity and clarification to the existing psychiatric exclusion criteria to directly address a history of psychoses or other psychiatric conditions that may be associated with a higher risk of psychosis	Prior versions of the protocol did contain psychiatric exclusion criteria. However, the further specificity and clarification will exclude patients with psychiatric disease who are not appropriate for participation in a clinical trial.
Section 6.3.4, Counsel regarding Safe Sex Practices	Added text to describe the content of counselling that should occur with participants	Counselling on safe sex practices leads to decreases in HIV-1 transmission.
Section 7.7, Concomitant	Added clarification on prohibited concomitant	Concomitant medications

Section # and Name	Description of Change	Brief Rationale
Therapy	medications	may have an interaction (as victim or perpetrator) with GSK3640254
Section 8.2, Withdrawal from the Study	Inserted new 2nd bullet to indicate that patients who are withdrawn from the study for reasons of safety should continue to be followed to assess the outcome of the safety event that triggered discontinuation of study drug.	For clarity
Section 12.2, Appendix 2, Clinical Laboratory Tests, Table 7	Inserted Amylase and Lipase tests to the Clinical Chemistry output	An improved safety monitoring for pancreas pathology complementing the pre-existing Lipase
Other administrative changes	Minor editorial and document formatting revisions	Minor, therefore not summarized

Amendment 03 26-AUG-2019

Summary of Changes

Synopsis, Objectives and Endpoints

PREVIOUS TEXT

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of GSK3640254 in HIV-1 infected TN participants during 10 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA)
Key Secondary	
• To assess the safety and tolerability of GSK3640254 when administered as monotherapy over 10 days in HIV-1 infected TN participants	• GSK3640254 safety and tolerability parameters: adverse events (AE); post-baseline values and changes over time of clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters
• To characterize the pharmacokinetics of GSK3640254 dosing for 10 days in HIV-1	• GSK3640254 PK parameters at the

Objectives	Endpoints
infected patients	following dose administration: **Day 1**: area under the plasma concentration time curve from zero to 24 (AUC [0-24]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag) Following repeat administration: Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC [0-τ]), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), apparent terminal phase half-life (t1/2), and apparent oral clearance (CL/F), if data permit.
• To explore the relationship between GSK3640254 exposure and change in plasma HIV-1 RNA	• GSK3640254 repeat-dose PK parameters AUC(0-τ), Cmax, Cτ with maximum HIV-1 RNA change from baseline
• To estimate GSK3640254 accumulation following administration of GSK3640254 for 10 days in HIV-1 infected patients.	• Accumulation: GSK3640254 PK accumulation ratios (R): repeat -dose AUC (0-τ), Cmax, and Cτ compared to Day 1 AUC (0-24), Cmax, C24, respectively
• To examine dose proportionality of GSK3640254 PK parameters following dosing for 10 days	• Relationship between Day 1 AUC (0-24), Cmax, C24, and repeat-dose AUC (0-τ), Cmax and Cτ and GSK3640254 dose levels

REVISED TEXT

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of GSK3640254 in HIV-1 infected TN participants during 10 days of monotherapy **in Part 1 and during 7 days of monotherapy in Part 2**	• Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA)
Key Secondary	
• To assess the safety and tolerability of GSK3640254 when administered as monotherapy over 10 **days in Part 1 and over 7 days in Part 2** in HIV-1 infected TN	• GSK3640254 safety and tolerability parameters: adverse events (AE); post-baseline values and changes over time of clinical laboratory evaluations, vital signs, and

Objectives	Endpoints
participants	electrocardiogram (ECG) parameters
• To characterize the pharmacokinetics of GSK3640254 dosing for 10 days **in Part 1 and for 7 days in Part 2** in HIV-1 infected patients	• GSK3640254 PK parameters at the following dose administration: **Day 1**: area under the plasma concentration time curve from zero to 24 (AUC [0-24]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag) Following repeat administration: Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC [0-τ]), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), apparent terminal phase half-life (t1/2), and apparent oral clearance (CL/F), if data permit.
• To explore the relationship between GSK3640254 exposure and change in plasma HIV-1 RNA	• GSK3640254 repeat-dose PK parameters AUC(0-τ), Cmax, Cτ with maximum HIV-1 RNA change from baseline
• To estimate GSK3640254 accumulation following administration of GSK3640254 for 10 **days in Part 1 and for 7 days in Part 2** in HIV-1 infected patients.	• Accumulation: GSK3640254 PK accumulation ratios (R): repeat -dose AUC (0-τ), Cmax, and Cτ compared to Day 1 AUC (0-24), Cmax, C24, respectively
• To examine dose proportionality of GSK3640254 PK parameters following dosing for 10 days **in Part 1 and for 7 days in Part 2**	• Relationship between Day 1 AUC (0-24), Cmax, C24, and repeat-dose AUC (0-τ), Cmax and Cτ and GSK3640254 dose levels

Synopsis, Overall Design (paragraphs 1 and 7, and Figure 1)

PREVIOUS TEXT

Paragraph 1:

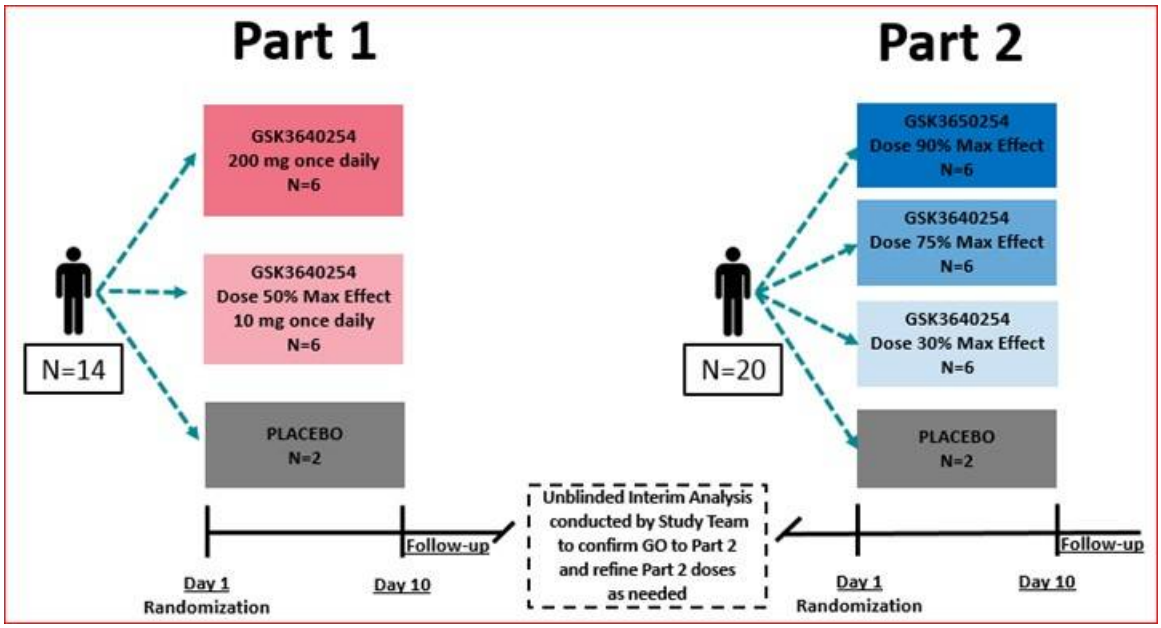
This is a Phase 2a, global, multicenter, randomized, double-blind (Sponsor-unblinded), placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability and PK/ pharmacodynamics (PD) of GSK3640254 over 10 days in ART-naïve HIV-1 infected adults, who are termed “participants” in rest of this protocol.

Paragraph 7:

In both Part 1 and Part 2, following a screening visit, qualified participants will be randomized within 14 days (up to 28 days in some cases) into one of the treatment arms,

each consisting of a 10-day treatment and minimum of 8 visits over 17 days. Then participants will receive follow-up evaluations during approximately 1-2 weeks following the last dose

Figure 1: 208132 Study Schematic



REVISED TEXT

Paragraph 1:

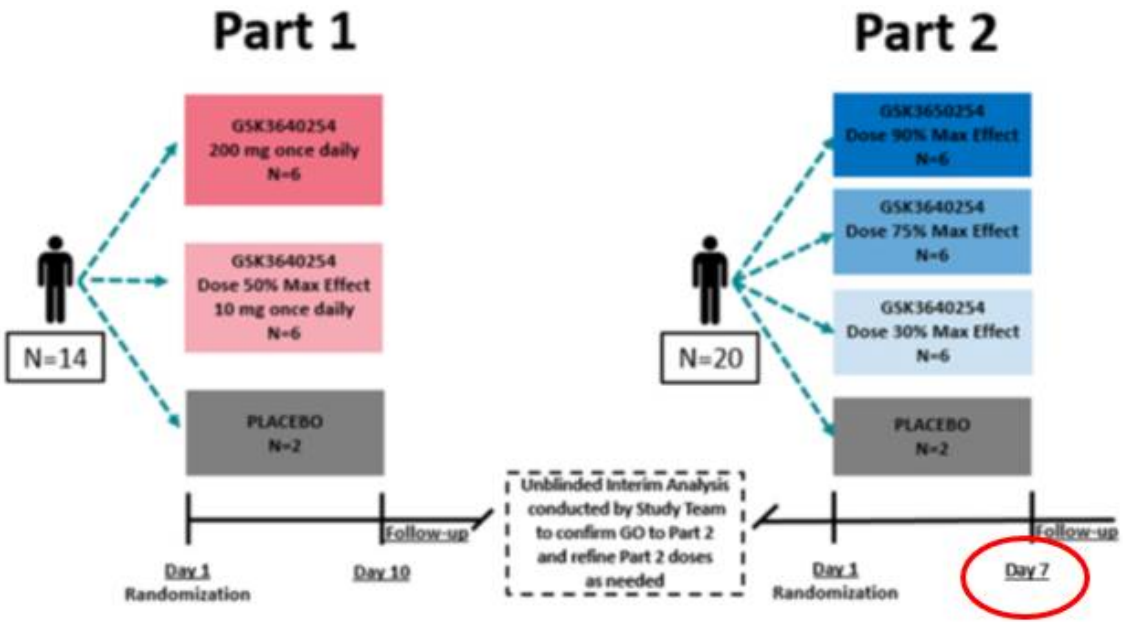
This is a Phase 2a, global, multicenter, randomized, double-blind (Sponsor-unblinded), placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability and PK/ pharmacodynamics (PD) of GSK3640254 over 10 days **in study Part 1 and over 7 days in study Part 2** in ART-naïve HIV-1 infected adults who are termed "participants" in rest of this protocol.

Paragraph 7:

In ~~both~~ **study** Part 1 ~~and Part 2~~, following a screening visit, qualified participants will be randomized within 14 days (up to 28 days in some cases) into one of the treatment arms, each consisting of a 10-day treatment and minimum of 8 visits over 17 days. Then participants will receive follow-up evaluations during approximately 1-2 weeks following the last dose.

In study Part 2, following a screening visit, qualified participants will be randomized within 14 days (up to 28 days in some cases) into one of the treatment arms, each consisting of a 7-day treatment and minimum of 6 visits over 8 days. Then participants will receive follow-up evaluations during approximately 3-5 days following the last dose.

Figure 1: 208132 Study Schematic



Synopsis, Treatment Groups and Duration, paragraphs 2-3, and paragraph 7 and onward

PREVIOUS TEXT

Paragraphs 2-3:

All participants will be screened for eligibility before being randomized, preferably within 14 days, into a 10-day treatment period. The 14-day screening period may be extended to 28 days in some cases to allow receipt of all screening results and/or to accommodate scheduling.

A qualified participant will be randomized into the treatment phase of the study and will administer study treatments, once daily, from Day 1 through Day 10. On Day 1, an appropriate number of bottles will be dispensed, with a supply sufficient to cover the entire 10-day treatment period. The blinded bottles will contain capsules of either the active dose or placebo. Dosing instructions will be indicated on each bottle. Participants will bring the bottles of study treatments to each visit, so that study treatment can be administered in the clinic after the study procedures have been performed.

REVISED TEXT

Paragraphs 2-3:

All participants will be screened for eligibility before being randomized, preferably within 14 days, into a 10-day treatment period **in Part 1 and into a 7-day treatment period in Part 2**. The 14-day screening period may be extended to 28 days in some cases to allow receipt of all screening results and/or to accommodate scheduling.

A qualified participant will be randomized into the treatment phase of the study and will administer study treatments, once daily, from Day 1 through Day 10 **in Part 1 and from Day 1 through Day 7 in Part 2**. On Day 1, an appropriate number of bottles will be dispensed, with a supply sufficient to cover the entire ~~10-day~~ treatment period. The blinded bottles will contain capsules of either the active dose or placebo. Dosing instructions will be indicated on each bottle. Participants will bring the bottles of study treatments to each visit, so that study treatment can be administered in the clinic after the study procedures have been performed.

PREVIOUS TEXT

Paragraph 7 and onward:

Participants will then enter the post-dosing period. There are 4 in-clinic visits in the post-dosing period: 3 visits for PK and other assessments during the 7 days immediately following the last dose, and a final follow-up visit primarily for safety (e.g., to follow any AEs to resolution) approximately 8-14 days after the last dose, as shown in the Schedule of Activities (SOA, Section 2). Participants should not start other medicines and will not start ARVs during the post-dosing period until they have completed the final follow-up visit.

In the shortest course, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in approximately 30 days (if, for example, only 10-14 days are needed for the screening period and the final follow-up visit is performed on Day 18).

In the longest course, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in 52 days (if, for example, 28 days are needed for the screening period and the final follow-up visit is performed on Day 24).

REVISED TEXT

Paragraph 7 and onward:

Participants will then enter the post-dosing period**:**

Study Part 1:

There are 4 in-clinic visits in the **Part 1** post-dosing period: 3 visits for PK and other assessments during the 7 days immediately following the last dose, and a final follow-up visit primarily for safety (e.g., to follow any AEs to resolution) approximately 8-14 days after the last dose, as shown in the **Part 1** Schedule of Activities (SOA, Section 2). **In Part 1, p**articipants should not start other medicines and will not start ARVs during the post-dosing period until they have completed the final follow-up visit.

In the shortest course **for Part 1**, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in approximately 30 days (if, for example, only 10-14 days are needed for the screening period and the final follow-up visit is performed on Day 18). In the longest course **for Part 1**, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in 52 days

(if, for example, 28 days are needed for the screening period and the final follow-up visit is performed on Day 24).

Study Part 2:
There are 2 in-clinic visits in the Part 2 post-dosing period: 1 visit for PK and other assessments on the day immediately following the last dose, and a final follow-up visit primarily for safety (e.g., to follow any AEs to resolution) 3-5 days after the last dose, as shown in the Part 2 Schedule of Activities (SOA, Section 2).

In Part 2, participants will start Investigator-selected, prescribed and provided cART immediately following the completion of the primary endpoint, i.e., the measurement of HIV-1 RNA on Day 8.

In the shortest course for Part 2, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow up visit) in approximately 24 days (if, for example, only 10-14 days are needed for the screening period and the final follow-up visit is performed on Day 10. In the longest course, a participant can be screened/qualified, treated and assessed for all the planned visits (including the final follow-up visit) in 40 days (if, for example, 28 days are needed for the screening period and the final follow-up visit is performed on Day 12).

Section 2.2, Part 1 and Part 2 Treatment, Post-Dosing and Follow-up Periods

PREVIOUS TEXT

A single table existed. No specific table existed for Part 2.

Previous Table Notes:

1. Procedures should be performed in the following order: ECG, Vitals, Blood Draws, followed by dose administration.
2. The study requires 9 in-clinic visits. Flexibility is offered for Visits 3, 4, 5, 8 and 9. The visit schedule for each participant should be pre-planned to be sure weekend, work schedules and clinic hours are appropriately considered. No visit interval during the treatment period can be greater than 3 days.
3. These assessments must be conducted with a participant during each day indicated, to include the days when the participant is not in the clinic. This can be done in via phone, preferably via a visual method (as locally permitted) of Skype, Facetime, WhatsApp, et. al.
4. Physical Exam will include, at a minimum, assessments of the Skin, Heart, Lungs, and Abdomen (liver and spleen).
5. Genotypic/Phenotypic testing will be conducted on Day 1 and Day 11 samples, with other visits tested as appropriate.
6. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits. These samples will be used when needed, such as when samples are lost or where quantity is insufficient for testing. In the event samples are not used by study completion, they will be utilized for additional research on ARV resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing)
7. If the Intensive PK day occurs on Day 10, do not collect the Day 11 pre-dose PK sample (as it is redundant with the 24-hr PK collection (completing the sample set started on Day 10).
8. Intensive Plasma PK samples will be collected as outlined in Table 4 in Section 9.5
9. If Day 8 or 9 is the Clinic Visit 5 to include the Intensive PK collection, the participant must return the following day for the 24-hr PK collection, meal and dosing. The assessments to be done as indicated on what is a "virtual visit day" should be captured as a virtual visit, even if the questions are asked in the clinic.
10. Log in to RAMOS on Day 1 to randomize the participant and to receive blinded study treatment. Subsequently log-in to RAMOS for study treatment supply as needed. If a participant is discontinued from the study early, log in to RAMOS to record the discontinuation

REVISED TEXT

In this amendment, the existing single table was given a label of ***Study Part 1:***

*A second table specific to study Part 2 was inserted and labelled as **Study Part 2:** The footnotes from Study Part 1 table were modified and inserted for Study Part 2 as shown below.*

Study Part 2:

Procedure[1]	Treatment Period Day 1 – Day 7							Post-Dosing Follow Up Period	Final Follow-up
	Day 1	Day 2	Day 3, 4 Choose one day for the Clinic Visit 3. The other day will be a virtual event.		Day 5, 6 Choose one day for the Clinic Visit 4. The other day will be a virtual event.		Day 7	Day 8	Day 10, 11 or 12
	Clinic Visit 1	Clinic Visit 2	Clinic Visit 3	Virtual	Clinic Visit 4	Virtual	Clinic Visit 5	Clinic Visit 6	Clinic Visit 7
Clinical Assessments									
Outpatient Visit[2]	X	X	X		X		X	X	X
Video/Phone Call				X		X			
Verify Inclusion/ Exclusion Criteria	X								
Medical/medication/drug/alcohol history	X								
Prior Anti-retroviral (ARV) Check	X								
CDC Classification	X								X

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
HIV-associated conditions assessments[3]	X	X	X	X	X	X	X	X	X
Adverse event (AE)/SAE assessment[3]	X	X	X	X	X	X	X	X	X
Concomitant medication review[3]	X	X	X	X	X	X	X	X	X
Weight, BMI and Physical exam[4]	X								
Vital Signs	X	X	X				X		X
C-SSRS Administration (*Since Last Visit* form)								X	

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Clinical Procedures									
12-lead ECG (triplicate reading, done pre-dose; single readings at PK draws 2hr, 4hr, and 6hr)	X								
12-lead ECG (single reading, done pre-dose at Visits 2 and 3)		X	X						X
12-lead ECG (single reading done pre-dose and at PK draws 2hr, 4hr, and 6hr)							X		

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Pharmacogenetics (PGX) Collection (if consented)	X								
Hematology/Chemistry/Urine	X	X	X		X		X	X	X
Fasting Lipid Panel (approximately 8 hrs)	X							X	X
Lymphocyte T-cell subsets (CD4, CD8)	X							X	
Plasma for HIV-1 genotype/phenotype[5]	X	X	X		X		X	X	
Plasma for storage[6]	X	X	X		X		X	X	X

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
HIV-1 RNA	X	X	X		X		X	X	X
Single, Pharmacokinetic (PK) sample done pre-dose			X		X				
Intensive PK sampling (to include the 24hr samples drawn the next day)	X						X		
Observed dosing with GSK3640254 /placebo[3]	X	X	X	X	X	X	X		

Procedure[1]	**Treatment Period Day 1 – Day 7**							**Post-Dosing Follow Up Period**	**Final Follow-up**
	Day 1	**Day 2**	**Day 3, 4** Choose one day for the Clinic Visit 3. The other day will be a virtual event.		**Day 5, 6** Choose one day for the Clinic Visit 4. The other day will be a virtual event.		**Day 7**	**Day 8**	**Day 10, 11 or 12**
	Clinic Visit 1	**Clinic Visit 2**	**Clinic Visit 3**	**Virtual**	**Clinic Visit 4**	**Virtual**	**Clinic Visit 5**	**Clinic Visit 6**	**Clinic Visit 7**
Observed dosing with Investigator-selected, prescribed and provided CART, and eCRF completion								X	
IWRS (RAMOS) activity[8]	X								

1 Procedures should be performed in the following order: ECG, Vitals, Blood Draws, followed by dose administration.

2 The study requires ~~9~~ **7** in-clinic visits. Flexibility is offered for Visits 3, 4,~~ 5, 8~~ and ~~9~~ **7**. The visit schedule for each participant should be pre-planned to be sure weekend, work schedules and clinic hours are appropriately considered. No visit interval during the treatment period can be greater than 3 days.

3 These assessments must be conducted with a participant during each day indicated, to include the days when the participant is not in the clinic. This can be done in via phone, preferably via a visual method (as locally permitted) of Skype, Facetime, WhatsApp, et. al.

4 Physical Exam will include, at a minimum, assessments of the Skin, Heart, Lungs, and Abdomen (liver and spleen).

5 Genotypic/Phenotypic testing will be conducted on Day 1 and Day ~~11~~ **8** samples, with other visits tested as appropriate.

6 Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits. These samples will be used when needed, such as when samples are lost or where quantity is insufficient for testing. In the event samples are not used by study completion, they will be utilized for additional research on ARV resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing)

~~7. If the Intensive PK day occurs on Day 10, do not collect the Day 11 pre-dose PK sample (as it is redundant with the 24 hr PK collection (completing the sample set started on Day 10).~~

7 Intensive Plasma PK samples will be collected as outlined in Table 4 in Section 9.5

~~9. If Day 8 or 9 is the Clinic Visit 5 to include the Intensive PK collection, the participant must return the following day for the 24-hr PK collection, meal and dosing. The assessments to be done as indicated on what is a "virtual visit day" should be captured as a virtual visit, even if the questions are asked in the clinic.~~

8 Log in to RAMOS on Day 1 to ~~**randomize the participant and to receive**~~ **dispense** blinded study treatment. Subsequently log-in to RAMOS for study treatment supply as needed. If a participant is discontinued from the study early, log in to RAMOS to record the discontinuation.

Section 3.1, Study Rationale

PREVIOUS TEXT

The proposed Study 208132 is a proof of concept (POC), randomized double blind (Sponsor-unblinded) study to characterize antiviral activity, safety/tolerability, PK, and the relationship between PK and antiviral activity of GSK3640254 given once daily (QD), administered across a range of doses over 10 days in HIV-1 infected treatment-naïve adults. To minimize the number of participants exposed to suboptimal or redundant doses, a two-part, adaptive and dose-ranging design is applied in this study. This two-part, adaptive design will allow an early understanding of the potential of GSK3640254, while not exposing HIV-infected participants to longer courses and possible development of resistance. Data from this study will be utilized to select doses for further studies in Phase 2b.

REVISED TEXT

The proposed Study 208132 is a proof of concept (POC), randomized double blind (Sponsor-unblinded) study to characterize antiviral activity, safety/tolerability, PK, and the relationship between PK and antiviral activity of GSK3640254 given once daily (QD), administered across a range of doses over 10 days **in study Part 1 and over 7 days in study Part 2** in HIV-1 infected treatment-naïve adults. To minimize the number of participants exposed to suboptimal or redundant doses, a two-part, adaptive and dose-ranging design is applied in this study. This two-part, adaptive design will allow an early understanding of the potential of GSK3640254, while not exposing HIV-infected participants to longer courses and possible development of resistance. Data from this study will be utilized to select doses for further studies in Phase 2b.

Section 3.2.2, Preliminary Safety and PK Data in Study 20718, Paragraph 6

PREVIOUS TEXT

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.

REVISED TEXT

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 ms or increases >60 ms from Baseline) observed for any participant in the SAD or MAD. A cardiodynamic evaluation of healthy subjects in the MAD portion of Study 207187 (placebo or GSK3640254 dose range 50 to 320 mg daily for 14 days) was performed. Serial ECGs were extracted from continuous Holter monitors at time-matched baseline on Day -1 and for approximately 24 hours post-dose on Days 1 and 14. In the concentration-QTc analysis, a final model with a treatment effect-specific intercept reasonably represented the data. The slope of the concentration-QTc relationship

was 0.004 ms per ng/mL (90% confidence interval [CI]: 0.0023 to 0.0048) with a small treatment effect-specific intercept of -0.9 ms (90% CI: -4.47 to 2.69). The QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD; note, the maximum dose used in Part 1 of this study, 208132, is 200 mg QD). Finally, there were no laboratory abnormality trends across doses that were clinically significant or associated with any symptoms.

Section 3.2.4, Justification for Part 2 Treatment Duration and Initiation of cART

PREVIOUS TEXT

No previous text.

REVISED TEXT

Data from Part 1 showed a decline in HIV-1 RNA and reasonable PK profile. There were no clinically significant trends in AEs, vital signs, ECG findings, or chemistry or haematology laboratory abnormalities across dosing arms. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on Day 11 (after 10 days of receiving GSK3640254 monotherapy). Additionally, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed at Day 11 as there is no known cross-resistance between maturation inhibitors and other classes of ARVs. Genotypic analysis of samples at Clinic Visit 5 (Study Day 8 or 9) revealed no treatment emergent resistance. As a result, VH made two substantial changes to decrease the risk of treatment emergent resistance to participants in study Part 2: 1) decrease the duration of monotherapy from 10 days to 7 days (based on the interim genotypic analysis), and 2) immediately start Investigator-selected cART at the completion of monotherapy at the Part 2 primary endpoint (HIV-1 RNA measured on Day 8).

Section 3.3, Benefit/Risk Assessment, Paragraph 1

PREVIOUS TEXT

Based upon pre-clinical and clinical studies with the prior MI GSK3532795, the major risks are GI intolerability (e.g. abdominal pain and diarrhoea), prolongation of QTc, and neuropsychiatric safety. The risk of GI intolerability and neuropsychiatric safety is described in Section 3.3.1. The risk for QTc prolongation is described below in Section 3.3.1 where one pre-clinical study did show one dog with an increased QTc interval when given a single dose of GSK3640254.

REVISED TEXT

Based upon pre-clinical and clinical studies with the prior MI GSK3532795, the major risks are GI intolerability (e.g. abdominal pain and diarrhoea) **and toxicity**, prolongation of QTc, ~~and~~ neuropsychiatric safety**, and treatment emergent resistance to GSK3640254. If present, preclinical GI toxicity findings (e.g. single cell parietal cell necrosis) in subjects would be minimal and not be persistent upon discontinuation of GSK3640254 after 7 days of dosing.** The risk of GI intolerability and neuropsychiatric safety is described in Section 3.3.1. The risk for QTc prolongation is described below in Section 3.3.1 where one pre-clinical study did show one dog with an increased QTc interval when given a single dose of GSK3640254. **As described in Section 3.2.2, a cardiodynamic analysis of healthy subjects in Study 207187 was conducted. A final model from the MAD data showed a QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD; note, 200 mg QD was the maximum dose used in Part 1 of this study 208132). Importantly, there were no abnormal clinically significant arrhythmias or QTc prolongations (values >500 ms or increases >60 ms from Baseline) in Study 207187. This study contains specific cardiac exclusion criteria, has ECG monitoring (at Tmax once GSK3640254 attains steady state concentration), and has QTcF based stopping criteria.**

Section 3.3.1, Risk Assessment

PREVIOUS TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3640254]		
Cardiovascular (QT prolongation)	Pre-clinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and Ltype calcium channel currents recorded from HEK 293 cells stably transfected with 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 one dog given 17 mg/kg. Later, there were no GSK3640254-related effects on ECG parameters in dogs given up to 25 mg/kg/day for 4 weeks. In the ongoing FTIH 208187 study, no participants to date have exhibited QTc change from baseline >60 msec or QTc > 500 msec.	Protocol exclusion criteria based on screening ECG parameters and cardiac medical history (see Section 6.2). Participants will have ECG monitoring during the course of the study (see SOA table) with QTc stopping criteria (see Section 8.1.2).
Gastrointestinal intolerability and toxicity	Clinical signs indicative of gastrointestinal intolerability (sporadic vomiting and abnormal faeces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells were present in preclinical species. These findings	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms (see Section 6.2) Participants will undergo continuous evaluation for adverse events during their participation in the trial; there are clinical stopping

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. The rates of GI AEs from the FTIH and RBA clinical trials (described above) are summarized in their respective synopses and the current Investigator Brochure.	criteria based upon intensity of treatment-emergent AEs (see Section 8.1.3). Finally, a GI toxicity evaluation and monitoring plan is available to guide the principal investigator (PI) should GI AEs emerge (see Section 9.4.6).
Neurologic/psychiatric safety	Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. From a Neurologic and Psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. The rates of Neurologic and Psychiatric AEs from the FTIH and RBA clinical trials (described above) are	Protocol exclusion criterion based on any preexisting psychiatric condition (including results of psychological assessment) for patients. Participants will have psychological assessment via a clinician (or qualified designee) administered C-SSRS in the study and will be included given no positive (abnormal) response. Continuous evaluation for adverse events during their participation in the trial including daily direct AE enquiry; The C-SSRS will also be administered after the treatment phase of the study. In the event of a positive (abnormal) response confirmed by the investigator, the patient will discontinue from the trial and the Principal Investigator/ Sub-Investigator (PI/SI) will arrange for urgent specialist psychiatric evaluation and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	summarized in their respective synopses and the current Investigator's Brochure.	management. Guidance for the PI on the management of emergent psychiatric symptoms are available (see Section 9.4.5) Finally, there are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 8.1.3).
HIV-1 Infection/Patient population		
HIV Resistance to GSK3640254	HIV-1 genotypic and phenotypic changes due to GSK3640254 monotherapy	Dosing is limited to 10 days of monotherapy to reduce the risk of emergent drug resistance. There are no commercially available/approved MIs nor is there evidence of cross-class resistance (e.g. protease inhibitors) therefore dosing with GSK3640254 will not interfere with selection of a cART regimen at the completion of the study. Strict adherence to protocol criteria around concurrent meds.

REVISED TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3640254]		
Cardiovascular (QT prolongation)	Pre-clinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and Ltype calcium channel currents recorded from HEK 293 cells stably transfected with 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 one dog given 17 mg/kg. Later, there were no GSK3640254-related effects on ECG parameters in dogs given up to 25 mg/kg/day for 4 weeks. ~~In the ongoing FTIH 208187 study, no participants to date have exhibited QTc change from baseline >60 msec or QTc > 500 msec.~~ **In the first time in human study 207187, no participant exhibited QTc change from baseline >60 ms or QTc >500 ms. As described in Section 3.2.2, in the concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD).**	Protocol exclusion criteria based on screening ECG parameters and cardiac medical history (see Section 6.2). Participants will have ECG monitoring during the course of the study (see SOA table) with QTc stopping criteria (see Section 8.1.2).
Gastrointestinal intolerability and toxicity	Clinical signs indicative of gastrointestinal intolerability (sporadic vomiting and abnormal faeces beginning on Day 1 and continuing	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms (see Section 6.2)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. The rates of GI AEs from the FTIH and RBA clinical trials (described above) are summarized in their respective synopses and the current Investigator Brochure.	Participants will undergo continuous evaluation for adverse events during their participation in the trial; there are clinical stopping criteria based upon intensity of treatment-emergent AEs (see Section 8.1.3). Finally, a GI toxicity evaluation and monitoring plan is available to guide the principal investigator (PI) should GI AEs emerge (see Section 9.4.6).
Neurologic/psychiatric safety	Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. From a Neurologic and Psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain	Protocol exclusion criterion based on any preexisting psychiatric condition (including results of psychological assessment) for patients. Participants will have psychological assessment via a clinician (or qualified designee) administered C-SSRS in the study and will be included given no positive (abnormal) response. Continuous evaluation for adverse events during their participation in the trial including daily direct AE enquiry; The C-SSRS will also be administered after the treatment phase of the study. In the event of a positive (abnormal) response confirmed by the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	distribution/penetration. The rates of Neurologic and Psychiatric AEs from the FTIH and RBA clinical trials (described above) are summarized in their respective synopses and the current Investigator's Brochure.	investigator, the patient will discontinue from the trial and the Principal Investigator/ Sub-Investigator (PI/SI) will arrange for urgent specialist psychiatric evaluation and management. Guidance for the PI on the management of emergent psychiatric symptoms are available (see Section 9.4.5) Finally, there are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 8.1.3).
HIV-1 Infection/Patient population		
HIV Resistance to GSK3640254	HIV-1 genotypic and phenotypic changes due to GSK3640254 monotherapy. **Data from Part 1 showed a decline in HIV-1 RNA and reasonable PK profile. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on Day 11 (after 10 days of receiving GSK3640254 monotherapy). Additionally, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed at Day 11 as there is no known cross-resistance between maturation inhibitors and other classes of ARVs. Genotypic**	Dosing is limited to 10 days of monotherapy **in Part 1** to reduce the risk of emergent drug resistance**, and additionally limited to 7 days of monotherapy in Part 2 to further reduce the risk of emergent MI drug resistance based on the genotypic analysis of the interim samples from Part 1.** There are no commercially available/approved MIs nor is there evidence of cross-class resistance (e.g. protease inhibitors) therefore dosing with GSK3640254 will not interfere with selection of a cART regimen at the completion of the **entire** study **(for Part 1) or the completion of the monotherapy portion of the study (Part 2).**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	analysis of samples at Clinic Visit 5 (Study Day 8 or 9) revealed no treatment emergent resistance.	Strict adherence to protocol criteria around concurrent meds.

Section 3.3.2, Benefit Assessment

PREVIOUS TEXT

This study in HIV-1 infected but otherwise healthy participants is a 10-day monotherapy design. There is no expected longer term anti-HIV benefit to administration of GSK3640254.

REVISED TEXT

This study in HIV-1 infected but otherwise healthy participants is a ~~10-day~~ **short term** monotherapy design. There is no expected longer**-**term anti-HIV benefit to administration of GSK3640254.

Section 3.3.3, Overall Benefit:Risk Conclusion

PREVIOUS TEXT

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy participants at the proposed GSK3640254 doses for 10 days is predicted to be low and manageable. Mean exposures at the highest dose studied are not projected to exceed lowest observed adverse effect level (LOAEL) values obtained in chronic toxicology studies, further reducing potential risk.

REVISED TEXT

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy participants at the proposed GSK3640254 doses, for 10 days **in Part 1 and for 7 days in Part 2**, is predicted to be low and manageable. Mean exposures at the highest dose studied are not projected to exceed lowest observed adverse effect level (LOAEL) values obtained in chronic toxicology studies, further reducing potential risk.

Section 4, OBJECTIVES AND ENDPOINTS

PREVIOUS TEXT

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of GSK3640254 in HIV-1-infected participants during 10 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 RNA
Secondary	
• To assess the safety and tolerability of GSK3640254 when administered as monotherapy over 10 days in HIV-1 infected participants	• GSK3640254 safety and tolerability parameters: adverse events(AE); post-baseline values and changes over time of clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters

Objectives	Endpoints
• To characterize the pharmacokinetics of GSK3640254 dosing for 10 days in HIV-1 infected patients	• GSK3640254 PK parameters at the following dose administration: Day 1: area under the plasma concentration time curve from zero to 24 (AUC [0-24]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag) Following repeat administration: Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC[0-τ]), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), apparent terminal phase half-life (t1/2), and apparent oral clearance (CL/F), if data permit.
• To explore the relationship between GSK3640254 exposure and change in plasma HIV-1 RNA	• GSK3640254 repeat-dose PK parameters AUC(0-τ), Cmax, Cτ with maximum HIV-1 RNA change from baseline
• To estimate GSK3640254 accumulation following administration of GSK3640254 for 10 days in HIV-1 infected patients.	• Accumulation: GSK3640254 PK accumulation ratios (R): repeat -dose AUC (0-τ), Cmax, and Cτ compared to Day 1 AUC (0-24), Cmax, C24, respectively
• To examine dose proportionality of GSK3640254 PK parameters following dosing for 10 days	• Relationship between Day 1 AUC (0-24), Cmax, C24, and repeat-dose AUC (0-τ), Cmax and Cτ and GSK3640254 dose levels
Exploratory	
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To assess attainment of steady state following administration of GSK3640254 for 10 days in HIV-1 infected patients.	• Steady State: pre-morning dose concentrations (C0) on Day 2 through Day 10 Cτ (Day 11)
• To assess the immunologic effects of GSK3640254 when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ T-cell count to Day 11
• To explore the relationship between GSK3640254 exposure and safety or immunologic parameters, if appropriate	• GSK3640254 repeat-dose PK parameters: AUC (0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count

Objectives	Endpoints
Note: Other exploratory objectives and endpoints may be specified in the Reporting and Analysis Plan (RAP).	

REVISED TEXT

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of GSK3640254 in HIV-1-infected participants during 10 days of monotherapy **in Part 1 and during 7 days of monotherapy in Part 2**	• Maximum change from baseline (Day 1) in plasma HIV-1 RNA
Secondary	
• To assess the safety and tolerability of GSK3640254 when administered as monotherapy over 10 days **in Part 1 and over 7 days in Part 2** in HIV-1 infected participants	• GSK3640254 safety and tolerability parameters: adverse events (AE); post-baseline values and changes over time of clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters
• To characterize the pharmacokinetics of GSK3640254 dosing for 10 days **in Part 1 and for 7 days in Part 2** in HIV-1 infected patients	• GSK3640254 PK parameters at the following dose administration: Day 1: area under the plasma concentration time curve from zero to 24 (AUC [0-24]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag) Following repeat administration: Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC[0-τ]), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), apparent terminal phase half-life (t1/2), and apparent oral clearance (CL/F), if data permit.
• To explore the relationship between GSK3640254 exposure and change in plasma HIV-1 RNA	• GSK3640254 repeat-dose PK parameters AUC(0-τ), Cmax, Cτ with maximum HIV-1 RNA change from baseline
• To estimate GSK3640254 accumulation following administration of GSK3640254 for 10 days **in Part 1 and for 7 days in Part 2** in HIV-1 infected patients.	• Accumulation: GSK3640254 PK accumulation ratios (R): repeat -dose AUC (0-τ), Cmax, and Cτ compared to Day 1 AUC (0-24), Cmax, C24, respectively
• To examine dose proportionality of	• Relationship between Day 1 AUC (0-

Objectives	Endpoints
GSK3640254 PK parameters following dosing for 10 days **in Part 1 and following dosing for 7 days in Part 2**	24), Cmax, C24, and repeat-dose AUC (0-τ), Cmax and Cτ and GSK3640254 dose levels
Exploratory	
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days **in Part 1 and over 7 days in Part 2** and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To assess attainment of steady state following administration of GSK3640254 for 10 days **in Part 1 and for 7 days in Part 2** in HIV-1 infected patients.	• Steady State: pre-morning dose concentrations (C0) on Day 2 through Day 10 Cτ (Day 11) **in Part 1 and on Day 2 through Day 7 Cτ (Day 8)**
• To assess the immunologic effects of GSK3640254 when administered over 10 days **in Part 1 and over 7 days in Part 2** in HIV-1 infected adults	• Change from baseline in CD4+ T-cell count to Day 11 **in Part 1 and to Day 8 in Part 2**
• To explore the relationship between GSK3640254 exposure and safety or immunologic parameters, if appropriate	• GSK3640254 repeat-dose PK parameters: AUC (0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count **in Part 1 and with Day 8 change from baseline in CD4+ cell count in Part 2**
Note: Other exploratory objectives and endpoints may be specified in the Reporting and Analysis Plan (RAP).	

Section 5.1, Overall Design, Paragraph 1

PREVIOUS TEXT

This is a Phase 2a, global, multicenter, double-blind (Sponsor-unblinded), randomized, placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability, PK and PD of GSK3640254 over 10 days in ART-naïve HIV-1 infected adults.

REVISED TEXT

This is a Phase 2a, global, multicenter, double-blind (Sponsor-unblinded), randomized, placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability, PK and PD of GSK3640254 over 10 days **in study Part 1 and over 7 days in study Part 2** in ART-naïve HIV-1 infected adults.

Section 5.1.1.1, Screening Phase

PREVIOUS TEXT

All participants will be screened for eligibility before being randomized, preferably within 14 days, into a 10-day treatment period. Randomization may occur as soon as all

Screening procedures have been completed and results are available and on file. The 14-day screening period may be extended (in some cases) to 28 days to allow receipt of all Screening assessment results and to accommodate scheduling.

REVISED TEXT

All participants will be screened for eligibility before being randomized, preferably within 14 days, into a 10-day treatment period **in study Part 1 and into a 7-day treatment period on study Part 2**. Randomization may occur as soon as all Screening procedures have been completed and results are available and on file. The 14-day screening period may be extended (in some cases) to 28 days to allow receipt of all Screening assessment results and to accommodate scheduling.

Section 5.1.1.2, Treatment Phase and Follow-up Phase

PREVIOUS TEXT

Participants will be required to attend 9 in-clinic visits throughout the duration of the study. Participant and Investigators will design a patient-centric visit schedule based on the optionality presented in the Schedule of Assessments (SOA; Section 2) to accommodate the 9 required visits over the (maximum) 24-day study period, and such that no visit interval exceeds more than 3 days.

Treatment Phase: Day 1 – Day 10

On Day 1, an appropriate number of bottles of study treatments will be dispensed with supply sufficient to cover the entire 10-day treatment period. The blinded bottles will contain capsules of either the active dose or placebo. Each bottle will indicate dosing instructions. Participants will bring the bottles of study treatments to each visit, so that they can be administered after the study procedures have been performed.

Participants will report to the clinic for visits in the morning of the days selected for each of the 5 visits in the treatment phase. Participants will arrive each day, with their study treatment container(s) and prior to administration of the morning dose, for safety and lab assessments, including ECGs and blood draws, as described in the SOA. Participants will be given morning doses in the clinic at each visit. On days when an in-clinic visit is not required, doses can be self-administered, and during observation by a site staff member using various forms of video calling (when at all possible and locally permitted) such as FaceTime, Skype, WhatsApp.

Two, serial, intensive blood PK sample collections will be done on Day 1, Clinic Visit 1 and on Day 9±1, Clinic Visit 5 (up to 24 hours post-morning dose). Participants will be required to fast for at least 8 hours [overnight] prior to the morning check-in for the intensive PK sampling visits. Participants will be required to stay in the clinic on Days 1 and 9±1 until all specified assessments are completed (12 hours post-dose). Participants will be required to return to the clinic the following morning to allow for the blood sampling at the 24-hr time point.

Study treatments should be administered near the same time each morning, within a 2-hr window.

Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories, with at least 120 calories from fat), that is required to be completed within 30 minutes just prior to dosing. A moderate calorie and fat breakfast is planned to be similar to the following (with additional meal suggestions in will be included in the Study Reference Manual [SRM]):

- 2 slices of bread
- 10 g of butter
- 20 gr of jam
- 15 g of cheese
- 175 mL of apple juice

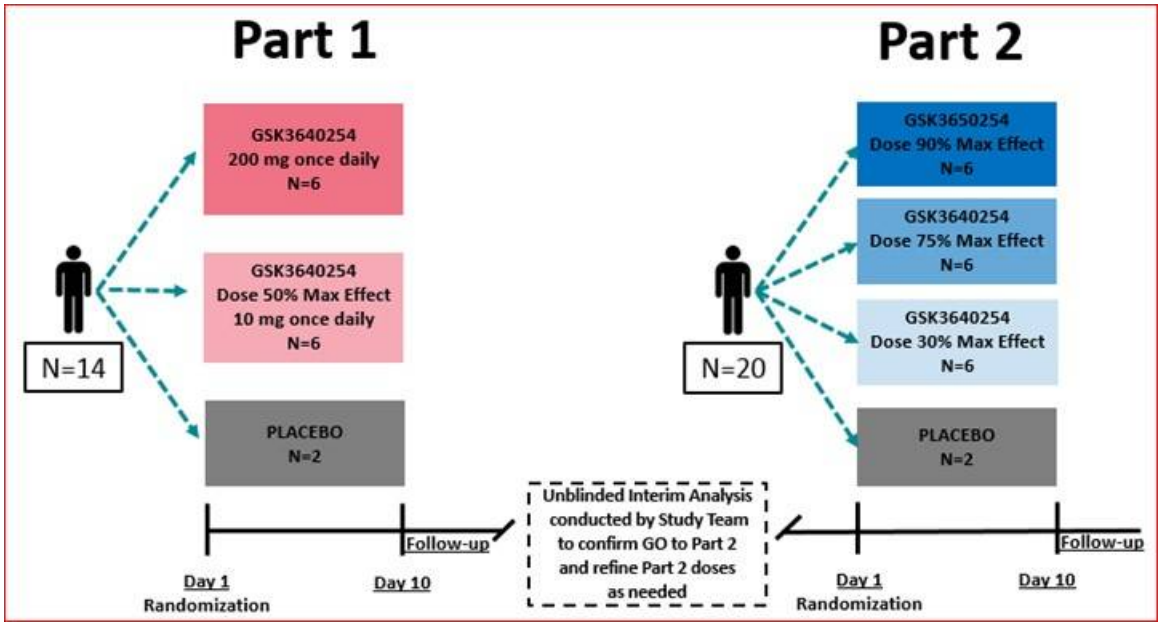
Follow-up Visits Day 11-17 and Final Follow-up Visit Day 18-24

Participants should not start other medicines and will not start ARVs during the post-dosing follow-up period until after the final follow-up visit has been completed.

Participants will return to the clinic in the post-dosing period for 4 visits (Visits 6-9).
- Three visits will be performed within the 7 days immediately following the dosing period for PK and measurement of assessments as shown in the SOA (Section 2).
- A final follow-up visit, to be performed approximately 8-14 days after the last dose, will be primarily for safety (e.g., to follow any AEs to resolution).

If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the participant for assessment of adverse events.

208132 Study Schematic



REVISED TEXT

Part 1:

Participants will be required to attend 9 in-clinic visits throughout the duration of the study in **Part** 1. Participant and Investigators will design a patient-centric visit schedule based on the optionality presented in the **Part 1** Schedule of Assessments (SOA; Section 2) to accommodate the 9 required visits over the (maximum) 24-day study period, and such that no visit interval exceeds more than 3 days.

Part 2:

Participants will be required to attend 7 in-clinic visits throughout the duration of the study in Part 2. Participant and Investigators will design a patient-centric visit schedule based on the optionality presented in the Part 2 Schedule of Assessments (SOA; Section 2) to accommodate the 7 required visits over the (maximum) 12-day study period, and such that no visit interval exceeds more than 3 days.

Treatment Phase: Day 1 – Day 10 in Part 1 and Day 1 – Day 7 in Part 2:

On Day 1, an appropriate number of bottles of study treatments will be dispensed with supply sufficient to cover the entire ~~10-day~~ treatment period. The blinded bottles will contain capsules of either the active dose or placebo. Each bottle will indicate dosing instructions. Participants will bring the bottles of study treatments to each visit, so that they can be administered after the study procedures have been performed.

Participants will report to the clinic for visits in the morning of the days selected for each of the 5 visits in the treatment phase. Participants will arrive each day, with their study treatment container(s) and prior to administration of the morning dose, for safety and lab assessments, including ECGs and blood draws, as described in the SOA. Participants will be given morning doses in the clinic at each visit. On days when an in-clinic visit is not required, doses can be self-administered, and during observation by a site staff member using various forms of video calling (when at all possible and locally permitted) such as FaceTime, Skype, WhatsApp.

Two, serial, intensive blood PK sample collections will be done on ~~Day 1,~~ Clinic Visit 1 and on ~~Day 9±1,~~ Clinic Visit 5 (up to 24 hours post-morning dose). Participants will be required to fast for at least 8 hours [overnight] prior to the morning check-in for the intensive PK sampling visits. Participants will be required to stay in the clinic ~~on Days 1 and 9±1~~ until all specified assessments are completed (12 hours post-dose). Participants will be required to return to the clinic the following morning to allow for the blood sampling at the 24-hr time point.

Study treatments should be administered near the same time each morning, within a 2-hr window.

Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories, with at least 120 calories from fat), that is required to be completed within 30 minutes just prior to dosing. A moderate calorie and fat breakfast is planned to be similar to the

following (with additional meal suggestions in will be included in the Study Reference Manual [SRM]):

- 2 slices of bread
- 10 g of butter
- 20 gr of jam
- 15 g of cheese
- 175 mL of apple juice

Follow-up Visits

Part 1:

Follow-up Visits Day 11-17 and Final Follow-up Visit Day 18-24

Participants should not start other medicines and will not start ARVs during the post-dosing follow-up period until after the final follow-up visit has been completed.

Participants will return to the clinic in the post-dosing period for 4 visits (Visits 6-9).

- Three visits will be performed within the 7 days immediately following the dosing period for PK and measurement of assessments as shown in the SOA (Section 2).
- A final follow-up visit, to be performed approximately 8-14 days after the last dose, will be primarily for safety (e.g., to follow any AEs to resolution).

If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the participant for assessment of adverse events.

Part 2:

Follow-up Visit Day 8 and Final Follow-up Visit Day 10-12

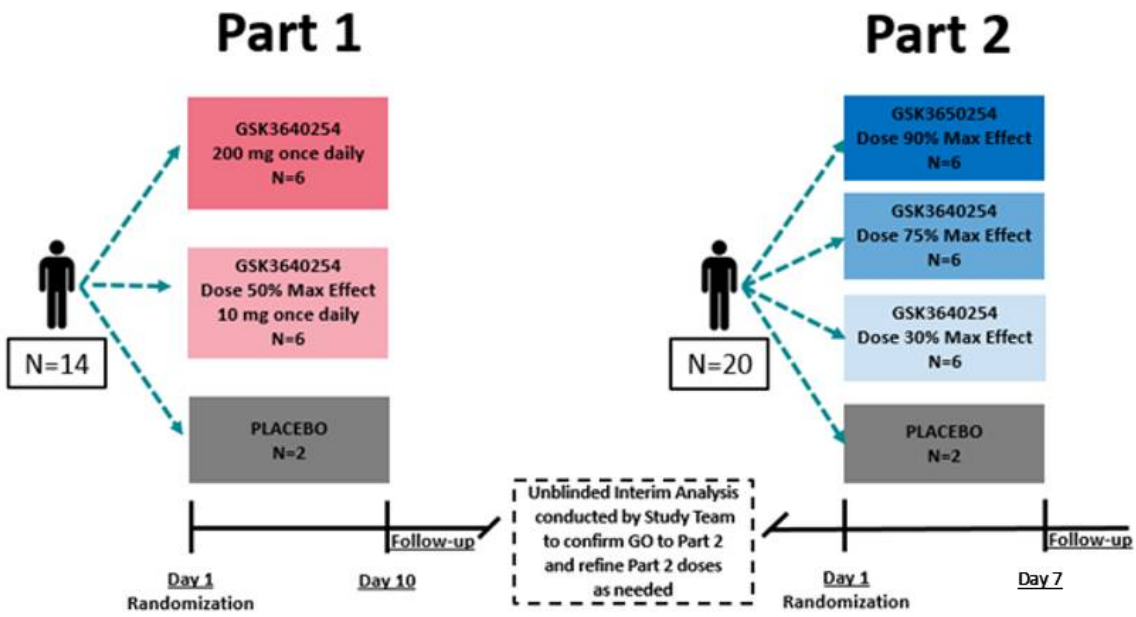
Participants should start Investigator-selected, prescribed and provided cART immediately in the post-dosing period on Day 8, after the blood collection is performed.

Participants will return to the clinic in the post-dosing period for 2 visits (Visits 6 and 7).

- **One visit will be performed on the day immediately following the dosing period for PK and measurement of assessments as shown in the SOA (Section 2).**
- **A final follow-up visit, to be performed approximately 3-5 days after the last dose, will be primarily for safety (e.g., to follow any AEs to resolution).**

If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the participant for assessment of adverse events.

208132 Study Schematic



Section 5.5, Dose Justification

PREVIOUS TEXT

The doses to be used in this study have been defined to adequately described the dose-exposure-response of GSK3640254 in treatment-naïve HIV patients. The doses were selected as to approximately provide a median effect of 30, 50, 75, 90 and 95% of the maximum anticipated effect on HIV-1 RNA for an MI drug in a 10-day study.

REVISED TEXT

The doses to be used in this study have been defined to adequately described the dose-exposure-response of GSK3640254 in treatment-naïve HIV patients. The doses were selected as to approximately provide a median effect of 30, 50, 75, 90 and 95% of the maximum anticipated effect on HIV-1 RNA for an MI drug in a **7-day or** 10-day study.

Section 6.1, Inclusion Criteria

PREVIOUS TEXT

None

REVISED TEXT

10. Participant must be willing and able to start cART on Study Day 8 (except in the case of early termination, clinically relevant AE/SAE, lab abnormality, the withdrawal of consent, lost to follow-up, etc., where circumstances could dictate otherwise)

Section 6.3.1, Meals and Dietary Restrictions, 1st Bullet

PREVIOUS TEXT

- Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories with at least 120 calories from fat), completed within approximately 30 minutes just prior to dosing. Prior to the two serial intensive blood PK collection days, to be done on Day 1 and on Day 9±1, participants will be required to fast for at least 8 hours [overnight] prior to the morning check-in.

REVISED TEXT

- Each dose of study medication will be taken with approximately 240 mL (8 ounces) of water following ingestion of a moderate calorie and fat meal (i.e. at least 400 calories with at least 120 calories from fat), completed within approximately 30 minutes just prior to dosing. Prior to the two serial intensive blood PK collection days, to be done on ~~Day 1~~**Clinic Visit 1** and on ~~Day 9±1~~**Clinic Visit 5**, participants will be required to fast for at least 8 hours [overnight] prior to the morning check-in.

Section 6.3.2, Alcohol, Tobacco and Marijuana

PREVIOUS TEXT

- During the study alcohol consumption will be limited to the following: An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.

No alcohol will be consumed on the in-clinic Intensive PK days (Day 1, Clinic Visit 1 and Day 9 ± 1, Clinic Visit 5), until after the final assessment of the day and release from the clinic.

- Only clinically minor to moderate use (as determined by the PI/SI) of tobacco products will be allowed during trial participation, with extremely limited use on the in-clinic Intensive PK days, (Day 1, Clinic Visit 1 and Day 9 ± 1, Clinic Visit 5).

- Subjects should refrain from the use of marijuana during the 10-day treatment period.

REVISED TEXT

- During the study alcohol consumption will be limited to the following: An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is

equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.

No alcohol will be consumed on the in-clinic Intensive PK days (~~Day 1,~~ Clinic Visit 1 and ~~Day 9 ± 1,~~ Clinic Visit 5), until after the final assessment of the day and release from the clinic.

- Only clinically minor to moderate use (as determined by the PI/SI) of tobacco products will be allowed during trial participation, with extremely limited use on the in-clinic Intensive PK days~~,~~ (~~Day 1,~~ Clinic Visit 1 and ~~Day 9 ± 1,~~ Clinic Visit 5).

- Subjects should refrain from the use of marijuana during the ~~10-day~~ treatment period.

Section 6.3.3, Activity

PREVIOUS TEXT

Participants should abstain from strenuous exercise during the 10-day treatment period.

REVISED TEXT

Participants should abstain from strenuous exercise during the ~~10-day~~ treatment period.

Section 7.8, Treatment and Care after the End of the Study

PREVIOUS TEXT

Given the lack of longer term clinical benefit (Section 3.3.2), VH recognizes the balance between the need to conduct an early phase monotherapy clinical trial (for the larger and long term unmet medical need) and the need for HIV-1 infected treatment naïve patients to receive cART as soon as possible after diagnosis. To meet both needs, this trial design is efficient in screening (shortest period: 14 days) and treatment/follow-up (shortest period: 18 days). A clinical trial commitment of as short as ~1 month is expected. After this time, VH expects all participating patients to receive local standard of care cART.

VH recognizes some HIV-1 infected adults may encounter barriers to accessing cART. Where it has been determined by the Investigator to be an acceptable option, participants receiving study treatment will have the option (but are not required) to receive reimbursement from the Sponsor for locally marketed ARVs (after the completion of 10 days of dosing and through the study final follow-up visit) for up to a maximum of 90 days. The selection of ARVs will be investigator-chosen based upon local standard of care.

The investigator is responsible for ensuring that participants will be referred for prompt cART initiation after completion of the study, whether or not VH is providing reimbursement for post-study treatment.

REVISED TEXT

Given the lack of longer term clinical benefit (Section 3.3.2), VH recognizes the balance between the need to conduct an early phase monotherapy clinical trial (for the larger and long term unmet medical need) and the need for HIV-1 infected treatment naïve patients to receive cART as soon as possible after diagnosis. To meet both needs, this trial design

is efficient in screening (shortest period: 14 days) and treatment/follow-up (shortest period: 18 days **in study Part 1 and 10 days in study Part 2**). A clinical trial commitment of as short as ~1 month is expected. After this time, VH expects all participating patients to receive local standard of care cART.

VH recognizes some HIV-1 infected adults may encounter barriers to accessing cART. Where it has been determined by the Investigator to be an acceptable option, participants receiving study treatment will have the option (but are not required) to receive reimbursement from the Sponsor for locally marketed ARVs (after the completion ~~of 10 days~~ of dosing and through the study final follow-up visit) for up to a maximum of 90 days. The selection of ARVs will be investigator-chosen based upon local standard of care.

The investigator is responsible for ensuring that participants will be referred for prompt cART initiation after completion of the study, whether or not VH is providing reimbursement for post-study treatment.

In the case of Part 2, participants will start Investigator selected, prescribed and provided cART immediately after the completion of the primary endpoint; i.e., specifically to be administered in the clinic on Day 8 after the blood collection has been performed.

Section 8.2, Withdrawal from the Study, final paragraph

PREVIOUS TEXT

If a participant withdraws from the study, he/she should complete a follow-up visit 7-14 days after treatment was stopped (Visit 9). If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the subject for assessment of adverse events.

REVISED TEXT

If a participant withdraws from the study, he/she should complete a follow-up visit 7-14 days after treatment was stopped (**conducted as a** Visit 9**) in study Part 1, and 3-5 days after treatment was stopped (conducted as a Visit 7) in study Part 2**. If a participant is unable to return to the clinic for any reason site staff are encouraged to contact the subject for assessment of adverse events.

Section 9.5, Pharmacokinetics, 2nd paragraph after bullets

PREVIOUS TEXT

Intensive PK sampling (Day 1, Clinic Visit 1 and Day 9±1, Clinic Visit 5) begins with a morning pre-dose sampling, i.e, prior to the administration of the morning dose of the study treatment on the day of the visit. The pre-dose sampling should be done approximately 24 hours after the morning doses of the study drugs were taken the day prior to the visit. This pre-dose blood sampling will include the collection of the other parameters as well.

REVISED TEXT

Intensive PK sampling (~~Day 1,~~ Clinic Visit 1 and ~~Day 9±1,~~ Clinic Visit 5) begins with a morning pre-dose sampling, i.e, prior to the administration of the morning dose of the study treatment on the day of the visit. The pre-dose sampling should be done approximately 24 hours after the morning doses of the study drugs were taken the day prior to the visit. This pre-dose blood sampling will include the collection of the other parameters as well.

Section 9.5, Pharmacokinetics, Table 4

PREVIOUS TEXT

Table 8 Intensive Pharmacokinetic Sampling Schedule and Other Activities at Day 1, Clinic Visit 1 and Day 9±1, Clinic Visit 5

	Time (Event)	**Window for blood draw**	**Time (Relative to Dosing) Hour: Min**
Day 1, Clinic Visit 1 And Day 9±1, Clinic Visit 5	morning pre-dose work: ECGs, vitals and full blood draw to include the pre-dose PK collection		
	Eat Meal. Administer study treatment and start the clock for subsequent blood draws.		00:00
	1 hr PK blood draw	± 5 minutes	01:00
	2 hr ECG and PK blood draw	± 15 minutes	02:00
	3 hr PK blood draw	± 15 minutes	03:00
	4 hr ECG and PK blood draw	± 15 minutes	04:00
	5 hr PK blood draw	± 15 minutes	05:00
	6 hr ECG and PK blood draw	± 15 minutes	06:00
	8 hr PK blood draw	± 30 minutes	08:00
	12 hr PK blood draw	± 2 hours	12:00
Next Day	24 hr (morning pre-dose) PK blood draw[1, 2]	± 2 hours	24:00
	Eat Meal and administer study treatment.		

1. This 24-hr pre-dose PK blood draw will be done at the same time as the collection for the lab kit on Day 2, Visit 2.

2. If the Visit 5 Intensive PK visit is done on Day 10, this 24-hr PK blood draw will be done at the same time as the collection for the lab kit on Day 11. Otherwise, this 24-hr blood draw is the only draw done on Day 9 (if the clinic visit is done on Day 8) or Day 10 (if the clinic visit is done on Day 9).

REVISED TEXT

Table 9 Intensive Pharmacokinetic Sampling Schedule and Other Activities at ~~Day 1,~~ Clinic Visit 1 and ~~Day 9±1,~~ Clinic Visit 5

	Time (Event)	**Window for blood draw**	**Time (Relative to Dosing) Hour: Min**
~~Day 1,~~ Clinic Visit 1 And ~~Day 9±1,~~ Clinic Visit 5	morning pre-dose work: ECGs, vitals and full blood draw to include the pre-dose PK collection		
	Eat Meal. Administer study treatment and start the clock for subsequent blood draws.		00:00
	1 hr PK blood draw	± 5 minutes	01:00
	2 hr ECG and PK blood draw	± 15 minutes	02:00
	3 hr PK blood draw	± 15 minutes	03:00
	4 hr ECG and PK blood draw	± 15 minutes	04:00
	5 hr PK blood draw	± 15 minutes	05:00
	6 hr ECG and PK blood draw	± 15 minutes	06:00
	8 hr PK blood draw	± 30 minutes	08:00
	12 hr PK blood draw	± 2 hours	12:00
Next Day	24 hr (morning pre-dose) PK blood draw[1, 2]	± 2 hours	24:00
	Eat Meal and administer study treatment.		

1. This 24-hr pre-dose PK blood draw will be done at the same time as the collection for the lab kit on ~~Day 2, Visit 2.~~**the next day**.
2. **In study Part 1, if** ~~If~~ the Visit 5 Intensive PK visit is done on Day 10, this 24-hr PK blood draw will be done at the same time as the collection for the lab kit on Day 11. Otherwise, this 24-hr blood draw is the only draw done on Day 9 (if the clinic visit is done on Day 8) or Day 10 (if the clinic visit is done on Day 9).

Section 9.8, Biomarkers, 2nd paragraph

PREVIOUS TEXT

Genotypic and phenotypic analyses will be carried out by using Gag/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the Gag/PR region will include susceptibility to GSK3640254. Analysis will be done on Day 1 and Day 11 samples initially, with other timepoints analyzed as data emerge for viral load response.

REVISED TEXT

Genotypic and phenotypic analyses will be carried out by using Gag/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the Gag/PR region will include susceptibility to GSK3640254. Analysis will be done on **samples collected in study Part 1 on** Day 1 and Day 11 ~~samples~~ initially**, and on samples collected in study Part 2 on Day 1 and Day 8 initially**, with other timepoints analyzed as data emerge for viral load response.

Section 10.1.1, Sample Size Considerations, 1st paragraph

PREVIOUS TEXT

The primary objectives of this study are to investigate the safety, tolerability and antiviral activity of GSK3640254 over a 10-day treatment period. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study

REVISED TEXT

The primary objectives of this study are to investigate the safety, tolerability and antiviral activity of GSK3640254 over a 10-day treatment **period in study Part 1 and over a 7-day treatment period in study Part 2**. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study

Section 10.3.2.3, Pharmacokinetic Analysis

PREVIOUS TEXT

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GSK. Plasma GSK3640254 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit:

Plasma GSK3640254 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	area under the plasma concentration time curve from zero to 24 AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag)
PART 1: Day 9±1	AUC(0-τ), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), half-life (t1/2), apparent oral clearance (CL/F).

Results based on samples collected from a participant with emesis within 6 hours of dosing will not be considered as evaluable.

All PK data will be stored in the R&D archives, GSK.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK3640254 PK parameters, with the exception of Tmax and Tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK3640254 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 9±1 [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using statistical analysis software (SAS) Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI.

The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 9±1 with Day 1 PK for each dose will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Visit 4 and 6 will be used for steady-state assessment.

REVISED TEXT

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GSK. Plasma GSK3640254 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit:

Plasma GSK3640254 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	area under the plasma concentration time curve from zero to 24 AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag)
PART 1: Day 9±1 **and PART 2: Day 7**	AUC(0-τ), Cmax, tmax, pre-dose concentration (C0), concentration at end of dosing interval (Cτ), half-life (t1/2), apparent oral clearance (CL/F).

Results based on samples collected from a participant with emesis within 6 hours of dosing will not be considered as evaluable.

All PK data will be stored in the R&D archives, GSK.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK3640254 PK parameters, with the exception of Tmax and Tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK3640254 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 9±1 **in study Part 1 and Day 7 in study Part 2** [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using statistical analysis software (SAS) Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI.

The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 9±1 with Day 1 PK for each dose **in Part 1 and comparisons of Day 7 with Day 1 PK for each dose in Part 2** will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Visit 4 and 6 will be used for steady-state assessment.

Section 12.2, Appendix 2: Clinical Laboratory Tests, Table 7, Under Clinical Chemistry, Glucose

PREVIOUS TEXT

Glucose (nonfasting)

REVISED TEXT

Glucose (non-fasting**)
****will be fasting on days when fasting lipids are collected.**