TITLE PAGE

Protocol Title: A two-period study in healthy male participants to determine the pharmacokinetics, balance/excretion, and metabolism of [^{14}C]-GSK3640254 following a single intravenous radiolabeled microtracer dose (concomitant with a non-radiolabeled oral dose) and a single oral radiolabeled dose

Protocol Number: 213051

Compound Number: GSK3640254

Study Phase: Phase 1

Short Title: Pharmacokinetics and metabolism of [^{14}C]-GSK3640254

Sponsor Name and Legal Registered Address:

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS, UK

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.

Regulatory Agency Identifying Number(s):

IND: 139,838 **EudraCT:** 2019-004444-30

Approval Date: 10-JUN-2020

PPD

From: PPD
Sent: Wednesday, June 10, 2020 8:23 PM
To: PPD
Subject: FW: Prot-213051-sponsign

From: Max Lataillade PPD
Sent: 10 June 2020 14:04
To: PPD
Cc: PPD
Subject: RE: Prot-213051-sponsign

I approve.
Best,
Max

From: PPD
Sent: Wednesday, June 10, 2020 7:29 AM
To: Max Lataillade PPD
Cc: PPD
Subject: Prot-213051-sponsign
Importance: High

Dear Sponsor,

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

PROTOCOL NUMBER: 213051

DOCUMENT IDENTIFIER: 2019N417919_01

AMENDMENT NUMBER: 01

PROTOCOL TITLE: A two-period study in healthy male participants to determine the pharmacokinetics, balance/excretion, and metabolism of [^{14}C]-GSK3640254 following a single intravenous radiolabeled microtracer dose (concomitant with a non-radiolabeled oral dose) and a single oral radiolabeled dose

Name of Sponsor Signatory: Max Lataillade

Title of Sponsor Signatory: VP and Head, Global Research Strategy, ViiV Research and Development

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 01	*10-JUN-2020*	*2019N417919_01*
Original Protocol	*11-MAR-2020*	*2019N417919_00*

Amendment [01] [10-JUN-2020]

Overall Rationale for the Amendment: The primary driver for the protocol amendment was to add the new rash risk. Following recent events involving COVID-19, additional changes around COVID-19 guidance was added.

Section # and Name	Description of Change	Brief Rationale
1.3 SoA	Minor typological changes. Daily temperature check added Withdrawal and discharge COVID-19 text	Minor typological changes. Daily temperature check added to follow GSK/ViiV COVID-19 guidelines. Withdrawal and discharge COVID-19 text
2.3.1 Risk Assessment	Addition of rash as potential risk of clinical significance.	In previous '254 clinical studies episodes of rash have been reported and some cases have led to study discontinuation. As a result, rash has been included as a risk for participants who are dosed with '254.
5.1 Inclusion Criteria	Upper age limit changed	Changed from 55 to 50 to follow GSK/ViiV COVID-19 guidelines
5.2 Exclusion Criteria	Liver chemistry updated 12 months changed to 3 years for monitoring occupation radiation exposure. WHO COVID-19 update	Liver chemistry updated as per the VSLC liver safety guidence April 2020. To ensure compliance with SOP 416111 'Enrolment of Human Subjects in Studies which involve their Exposure to Ionising Radiation'. Addition of WHO COVID-19 exclusion guidance
7.1.5 Discontinuation of Study Intervention	Addition of COVID-19 as discontinuation criteria.	Addition of moderate or severe COVID-19 infection as discontinuation criteria.
8.3 Adverse Events and Serious Adverse Events	Reference to Appendix for AE's and SAE's related to COVID-19	Reference to Appendix for AE's and SAE's related to COVID-19.
9.7 Other Analyses	Addition of special statistical and data analysis considerations.	Special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity.
10.9 COVID-19 Pandemic and Clinical Trial	Addition of appendix to document requirements to mitigate for any	This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety,

Section # and Name	Description of Change	Brief Rationale
Continuity	actions related to COVID-19	welfare and rights, and to ensure data integrity and the integrity of the clinical trial, as a result of COVID-19 only.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A two-period study in healthy male participants to determine the pharmacokinetics, balance/excretion, and metabolism of [^{14}C]-GSK3640254 following a single intravenous radiolabeled microtracer dose (concomitant with a non-radiolabeled oral dose) and a single oral radiolabeled dose

Short Title: Pharmacokinetics and metabolism of [^{14}C]-GSK3640254

Rationale:

Absorption, metabolism and excretion of GSK3640254 have been studied in pre-clinical animal models, in vitro, and in previous clinical trials. However, no dedicated clinical studies of drug absorption, metabolism, and excretion have been conducted for GSK3640254. Using radiolabelled GSK3640254 with Accelerator Mass Spectrometry (AMS) will enable quantitative measurement of GSK3640254 concentrations and comprehensive identification and quantification of drug metabolites that would not otherwise be possible.

This open-label study in 6 healthy male participants will assess the pharmacokinetics, balance/excretion, and metabolism of GSK3640254 in humans using [^{14}C]-radiolabelled drug substance administered as an intravenous (IV) infusion and orally. [^{14}C]-GSK3640254 administered by IV infusion will be a microtracer dose; therefore, it will be administered concomitantly with an oral non-radiolabelled dose, to ensure that the pharmacokinetics (PK) are representative of a clinically-relevant dose. Use of a bile string collection device for sampling duodenal bile after IV infusion and oral dose of [^{14}C]-GSK3640254 will enable a qualitative assessment of drug metabolites in this matrix to characterise biliary elimination pathways. The study will also provide an assessment of GSK3640254 absorption, metabolism and excretion following administration of a [^{14}C]-radiolabelled oral suspension.

Objectives and Endpoints:

Objectives	Endpoints[1]
Primary	
• To determine parent GSK3640254 and total drug-related radioactivity systemic concentrations following a single IV microtracer dose of [^{14}C]-GSK3640254 (with an oral dose of non-radiolabelled GSK3640254) and oral dose of [^{14}C]-GSK3640254[1]	• AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) in plasma and blood. • Volume of distribution at steady state (Vss) and clearance (CL) of parent after IV dose (Period 1 only). • Renal clearance of parent (CLr) after both IV and oral dose • Oral clearance (CL/F) and apparent volume of distribution (Vz/F) for the parent following oral administration
• To calculate the absolute oral bioavailability of GSK3640254	• Direct estimation of absolute oral bioavailability (F), indirect calculation of fraction of drug escaping first pass hepatic clearance (Fh), fraction absorbed (Fa) and fraction of drug escaping gut metabolism (Fg).
• To determine the rate and extent of excretion of total radioactivity in urine and feces and the total recovery of radioactivity, following IV and oral administrations of [^{14}C]-GSK3640254	• Urinary and fecal cumulative excretion as a percentage of the total radioactive dose
Secondary	
• To evaluate the safety and tolerability of GSK3640254 after single IV and oral doses in healthy participants.	• Characterize observed adverse events, and abnormal laboratory, 12-lead ECG, and vital signs assessments observed.
• To determine the blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity) associated with blood cellular components	• Blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity).
Exploratory	
• To generate samples that will be used to characterize the metabolite profile of GSK3640254 following a single IV microtracer dose of [^{14}C]-GSK3640254	• Characterization and quantification of metabolites in plasma, urine, feces, and duodenal bile (qualitative identification in bile). These analytical investigations will be

Objectives	Endpoints[1]
concomitant with an oral dose of non-radiolabelled GSK3640254 (plasma, urine, feces, duodenal bile) and a single, oral dose of [^{14}C]- GSK3640254 (plasma, urine, feces, duodenal bile).	conducted, and the results reported under a separate nonclinical GSK protocol.
• To evaluate the PK and relative bioavailability of GSK3640254 following administration of the 85 mg suspension compared to the 200 mg tablet	• AUC(0-inf), AUC(0-t) and Cmax

AUC(0–inf): Area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinite time, AUC(0–t): Area under the plasma concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments, Cmax: Maximum observed plasma concentration, tmax: time of occurrence of Cmax, t1/2: terminal phase half-life, ECG: electrocardiogram.

[1] For measured concentrations of GSK3640254 in plasma, the nomenclature **[^{14}C]-GSK3640254** describes the parent GSK3640254 concentration derived via analysis by liquid chromatography (LC) + AMS, whereas **GSK3640254** describes the parent GSK3640254 concentration derived via liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Overall Design:

This open-label, single-center, non-randomised, 2-period, single-sequence, mass balance study will enroll a cohort of 6 healthy male participants. The pharmacokinetics, balance/excretion, and metabolism of GSK3640254 will be assessed across two treatment periods. In Treatment Period 1, [^{14}C]-radiolabelled drug substance will be administered as an IV infusion of a microtracer dose along with an oral tablet, non-radiolabelled dose. In Treatment Period 2, [^{14}C]-radiolabelled drug substance will be administered orally.

Disclosure Statement: This is a single group, single center, [^{14}C]-GSK3640254 mass balance study with a two-period, single sequence and no blinding.

Number of Participants: Approximately six participants will be enrolled to achieve at least 4 participants completing the two treatment periods.

Replacement participants will be sought if it is likely the total number of participants who complete dosing and all critical assessments will drop below 4. Any replacement participants will be required to complete both treatment periods.

Intervention Groups and Duration:

Each participant will be involved in the study for up to 10 weeks. Each participant will have:

- A screening visit (up to 30 days before first dose)
- Two inpatient treatment periods (Treatment Periods 1 and 2), with at least 13 days between doses.
- A follow-up or early withdrawal visit 7 – 14 days after the last assessment performed.

During both treatment periods, participants will reside in the unit from Day -1 until all procedures are completed 168 h post-dose on Day 8. Participants may be asked to stay for up to 1 week longer in Treatment Period 2, if required, to demonstrate sufficient recovery of drug-related material. Thereafter, if deemed necessary to demonstrate sufficient recovery of radioactivity, participants may be asked to collect excreta at home.

Data Monitoring Committee: No

Treatment Period 1 (oral tablets and ^{14}C-intravenous infusion)

On Day 1 of Treatment Period 1, after an overnight fast of at least 8 h, each participant will take a single 200 mg oral dose (2 x 100 mg tablets) of GSK3640254 with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat); the IV infusion of 100 µg of [^{14}C]-GSK3640254 (approximately 3.7 kBq; 100 nCi) will begin 5 h after oral dose and continue over 1 h. Blood samples, all voided urine, and feces will be collected continuously from Day 1 through Day 8, while duodenal bile will be collected as described below. Participants will be discharged on study Day 8 after completion of the 168-h sample collection and other planned assessments and instructed to return to the clinic on Day 1 of Treatment Period 2.

A non-invasive device (Entero-tracker) to collect duodenal bile will be used in Treatment Period 1. The bile string will be swallowed 2 h after the oral dose and 3 h before the IV infusion starts, a duration recommended to allow transit of the string to the duodenum. Participants will fast from insertion of the bile string until the completion of the IV infusion, at which point a food cue (small standard high-fat meal) will be given to stimulate gall bladder emptying. The Entero-tracker will be removed about 1.5 h after the IV infusion stops (7.5 h after the oral dose).

Treatment Period 2 (^{14}C-oral suspension)

On Day 1 of Treatment Period 2, after an overnight fast of at least 8 h, each participant will receive approximately 85 mg [^{14}C]-GSK3640254 (approximately 3.15 MBq; 85 µCi) as an oral suspension with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat). A non-invasive device (Entero-tracker) to collect duodenal bile will be used in Treatment Period 2. The Entero-tracker will be swallowed 2 h after oral dose. At 5.5 h after the start of oral dose, a food cue (small standard high-fat meal) will be given to stimulate gall bladder emptying. The collection bile string will be removed 1.5 h post the food cue (7 h after the oral dose) to capture the duodenal bile samples expelled from the gall bladder.

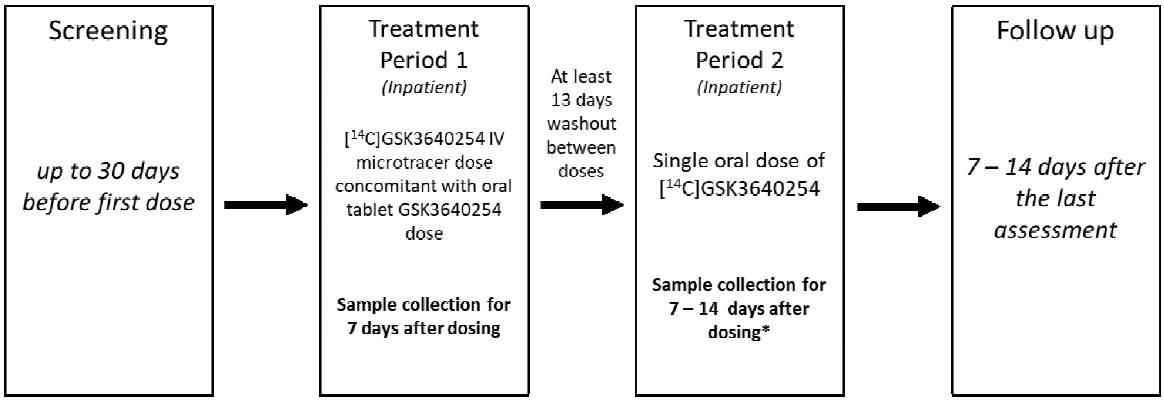
Blood, urine and fecal samples will be collected continuously from Day 1 through Day 8. Radioactivity quantification using liquid scintillation counting (LSC) will be performed on each 24-h urine collection and each 24-h fecal homogenate. Criteria for discharge for Period 2 are based on demonstrated cumulative recovery of radioactivity >90% or <1% in two consecutive samples The inpatient stay may be extended by up to 7 days to meet the discharge criteria. In the unlikely event that excretion is still >1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect fecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

Total Radiation Exposure

The total amount of radiation exposure in the study is ~3.15 MBq (~85.1 μCi).

1.2. Schema

Figure 1 Study Intervention Schematic



*If radioactivity in the 24 hour interval collections immediately prior to discharge is still >1%, faecal samples will be collected by participants at home after Day 15 (day of discharge/follow up)

1.3. Schedule of Activities (SoA)

The timing and number of planned study assessments, including safety and pharmacokinetic assessments, may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. Participants who withdraw from the study early should be subject to those assessments that would be required at discharge in that treatment period, if participants agree.

Participants who are withdrawn and discharged from the study due to COVID-19 infection will return to the site for follow up assessments after 2 weeks.

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent (ICF).

If assessments are scheduled for the same nominal time, the assessments should occur in the following order:

1. vital signs
2. 12-lead electrocardiogram (ECG)
3. blood draws
4. other assessments

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Table 1 SoA Screening, Follow up and Early Withdrawal

Procedure	**Screening**[1] *(Up to 30 days before first dose)*	**Follow up/Early Withdrawal** *(7 – 14 days after the last assessment)*	**Comments**
Informed consent	X		
Medical history (including drug/alcohol use)	X		
Demography	X		
12-lead ECG	X	X	Single ECG measurements will be obtained at screening. Repeats can be obtained if the original reading cannot be interpreted. See Section 8.2.
Vital signs	X	X	Single measurements will be obtained for all parameters. Repeats can be obtained if the original reading cannot be interpreted. See Section 8.2.
Drugs of abuse screen	X		
Alcohol, cotinine, & CO breath tests	X		
HIV and hepatitis B and C screen	X		
Laboratory safety tests (incl. LFTs)	X	X	
Physical exam	X-full	X-brief	Details of full and brief physical exams in Section 8.2.1
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	Details included in Section 8.2.5
Blood samples for total background radioactivity	X		
AE/SAE and concomitant meds review	X	X	AEs will be collected from the start of study intervention until the final follow-up visit. All SAEs will be recorded from the time each participant consents to participate in the study

Abbreviations: AE: adverse event; ECG: electrocardiogram; HIV: human immunodeficiency virus; LFTs: liver function tests; SAE: serious adverse event

Table 2 SoA: Treatment Period 1 (oral tablets and ^{14}C-labelled intravenous infusion)

Procedure	Day -1	Day 1 (hours)																				2		3	4	5	6	7	8	Notes
		Pre dose	0		1		2	3	4		5			6	7		8	9	10	12	24	36	48	72	96	120	144	168		
			.0	.5	.0	.5			.0	.5	.0	.25	.5		.0	.5														
Admission	X																													
Discharge																													X	
12-lead ECG	X	X					X	X	X		X			X								X				X			X	Single measurements for all timepoints except pre-dose which should be taken in triplicate. See Section 8.2.
Vital signs	X	X							X																				X	Single measurements will be obtained for all parameters. Repeats can be obtained if the original reading cannot be interpreted. See Section 8.2.
Temperature Check																						X		X	X	X	X	X		Single for all measurements.
Drugs of abuse screen	X																													
Alcohol, cotinine, & CO breath tests	X																													
Laboratory safety tests	X																					X				X			X	See Appendix 2 for details.
Brief Physical	X																												X	See Section 8.2.1
Columbia-Suicide Severity Rating Scale	X																												X	See Section 8.2.5

Procedure	Day -1	Day 1 (hours)																					2	3	4	5	6	7	8	Notes
		Pre dose	0		1		2	3	4		5			6	7		8	9	10	12	24	36	48	72	96	120	144	168		
			.0	.5	.0	.5			.0	.5	.0	.25	.5		.0	.5														
Entero tracker							X									X													See Section 8.5.5
Oral GSK3640254			X																											Participants will fast for at least 8 h before oral dosing.
14C-GSK3640254 IV											⟷																			1 hour long IV infusion to start 5 h after oral dose
Monitor local IV tolerability											⟷																			To be monitored during 1 h long infusion
Meal			X											X																Meal time is specified for Day 1 breakfast and mid-day only. On all other days, meals will be served at the unit's standard times. Refer to Section 5.3.1.
Blood samples for plasma total radioactivity, PK and metabolite ID	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		From this sample, background radiation will be measured on admission (Day –1), and pre-dose on Day 1. See Section 8.5.1
Fecal collection	X			⟷																										See Section 8.5.3
Urine collection		X		⟷																										See Section 8.5.2
AE/SAE/Concomitant med. review	⟷																													See Section 8.3

Abbreviations: AE: adverse event; ECG: electrocardiogram; IV: intravenous; LFTs: liver function tests; PK: Pharmacokinetic; SAE: serious adverse event.

Table 3 SoA: Treatment Period 2 (^{14}C-labelled oral suspension)

Procedure	Day -1	Day 1 (hours)																	2		3	4	5	6	7	8	Notes
		Pre-dose	0		1		2	3	4		5		6	7	8	10	12	24	36	48	72	96	120	144	168		
			.0	.5	.0	.5			.0	.5	.0	.5															
Admission to unit	X																										
Discharge from unit																										X	Discharge will be contingent upon demonstration of adequate recovery of radioactivity (see Section 4.1.3). If discharge is delayed all Day 8 assessments should be performed on day of discharge.
12-lead ECG	X	X					X	X	X		X		X						X				X			X	Single measurements for all timepoints except pre-dose which should be taken in triplicate. See Section 8.2.3 for ECG details.
Vital signs	X	X							X																	X	Single for all measurements.
Temperature check																			X		X	X	X	X	X		Single for all measurements.
Drugs of abuse screen	X																										
Alcohol, cotinine, & CO breath tests	X																										
Laboratory safety tests)	X																		X				X			X	
[^{14}C]-GSK3640254 oral suspension			X																								
Brief physical exam	X																									X	See Section 8.2.1
Columbia-Suicide Severity Rating Scale	X																									X	See Section 8.2.5

Procedure	Day -1	Day 1 (hours)																	2		3	4	5	6	7	8	Notes
		Pre-dose	0		1		2	3	4		5		6	7	8	10	12	24	36	48	72	96	120	144	168		
			.0	.5	.0	.5			.0	.5	.0	.5															
Entero tracker							X							X													See Section 8.5.5
Defined meal		X										X															Meal time is specified for Day 1 breakfast and mid-day only. On all other days, meals will be served at the unit's standard times. Refer to Section 5.3.1.
Blood samples for plasma total radioactivity, PK and metabolite ID		X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		See Section 8.5.1
Blood samples for blood/plasma ratio and metabolite ID							X		X				X		X	X											2 mL blood samples for measuring total radioactivity in whole blood to calculate blood/plasma ratio. At 4 h only a 10 mL sample will be obtained for metabolite ID.
Urine collection		X	←															→									See Section 8.5.2
Fecal collection		X	←															→									See Section 8.5.3
AE/SAE/ concomitant medication review		←																→									See Section 8.3

Abbreviations: AE: adverse event; ECG: electrocardiogram; LFTs: liver function tests; SAE: serious adverse event

2. 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 MIs approved for the treatment of HIV infection.

2.1. Study Rationale

This study will assess the pharmacokinetics, balance/excretion, and metabolism of GSK3640254 in humans using [^{14}C]-radiolabelled drug substance administered as an IV infusion and orally. [^{14}C]-GSK3640254 administered by IV infusion will be a microtracer dose; therefore, it will be administered concomitantly with an oral non-radiolabelled dose, to ensure that the PK are representative of a clinically-relevant dose. Use of a string bile collection device (Entero-tracker) for sampling duodenal bile after IV [^{14}C]-GSK3640254 infusion will enable a qualitative assessment of drug metabolites in this matrix to characterise biliary elimination pathways.

Absorption, metabolism and excretion of GSK3640254 have been studied in pre-clinical animal models, *in vitro*, and in previous clinical trials. However, no dedicated clinical studies of drug absorption, metabolism, and excretion have been conducted for GSK3640254. Using radiolabelled GSK3640254 with Accelerator Mass Spectrometry (AMS) will enable quantitative measurement of GSK3640254 concentrations and comprehensive identification and quantification of drug metabolites in plasma that would not otherwise be possible.

2.2. Background

GSK3640254 is an HIV MI which is improved over prior developmental MIs in the following ways: (1) it exhibits significantly improved pan-genotypic coverage and potency against polymorphic variants; (2) *in vitro* data suggest that GSK3640254 exhibits a higher barrier to emergence of resistant viruses (except for A364V); (3) GSK3640254 has improved potency in vitro toward all HIV-1 subtypes; and (4) it has a projected lower once-daily human dose (see Dose Justification, Section 4.3).

A detailed description of the chemistry, pharmacology, drug metabolism and pharmacokinetics (DMPK) and safety of GSK3640254 is provided in the Investigator Brochure (IB) (see GSK Document Number 2018N379610_01).

2.3. Benefit/Risk Assessment

As of 24 August 2019, an estimated 143 participants have been exposed to GSK3640254. This includes healthy participants or HIV-1 infected treatment naïve patients across 6 randomized clinical studies: Phase 1 studies (207187 [Part 1 and 2], 208131, 209712, 208134 and ongoing study 208135) and Phase 2a Study 208132 (Part 1). A detailed

summary of the above-mentioned studies, along with more information about the known and expected risks, and reasonably expected AEs associated with GSK3640254 can be found in the IB. Risks, along with their mitigation plans are outlined in the table below. Finally, there are no benefits to individuals participating in this trial.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention: GSK3640254	
Prolongation of QT interval	Preclinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with complementary Deoxyribonucleic acid (DNA) from the ion channels. In a single-dose safety pharmacology study in telemeterized dogs, increases in QT interval (up to 20 ms) occurred primarily in 1 dog given 17 mg/kg. Later, there were no GSK3640254-related effects on 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 corrected QT interval (QTc) change from Baseline >60 ms or QTc >500 ms. In the concentration- QTc analysis, a QT duration corrected for heart rate by Fridericia's formula (QTcF) effect above 10 ms could be excluded for GSK3640254 plasma concentrations of up to approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD).	• Protocol exclusion criteria based on Screening ECG parameters and cardiac medical history. • Participants will have ECG monitoring during the course of the study with QTc stopping criteria.
Gastrointestinal (GI) intolerability	Clinical signs indicative of GI intolerability (sporadic vomiting and abnormal feces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells were present in preclinical species. These findings were reversible. Gastrointestinal intolerability (predominantly abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795, which was evaluated through Phase 2b dosing. In the multiple ascending dose part of the first time in human Study 207187, clinically relevant GI AEs (abdominal pain lower, diarrhoea, feces soft, gastro-esophageal reflux disease, nausea, abdominal distention, and abdominal pain) were experienced by 9 participants. The greatest incidences were in the GSK3640254 200 mg arms (Cohorts 5 and 7) but ultimately, no dose/AE relationship was apparent. One participant each in the GSK3640254 200 mg arm and 320 mg arm reported nausea (mild in intensity), considered by the investigator in each case to be related to study drug.	• Protocol exclusion criterion based on pre-existing GI pathology or Baseline GI signs/symptoms. • Participants will undergo continuous evaluation for AEs during their participation in the study; there will be individual clinical stopping criteria based upon intensity of treatment-emergent AEs. A GI toxicity evaluation and monitoring plan will be available to guide investigators should GI AEs emerge. (see Section 8.2.6)
Neurologic/psychiatric safety	Two psychiatric SAEs in previous maturation inhibitor GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) were seen at supratherapeutic doses in healthy participants in the thorough QT (TQT) study. From a neurologic and psychiatric AE summary and PK/pharmacodynamic analysis for	• Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment) for participants. Participants will have a clinician (or qualified designee) administered C-SSRS and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK3532795 across all studies, Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and Phase 2b studies). No exposure-response relationship was seen for select neurologic and psychiatric AEs (based on TQT and Phase 2b studies). Central nervous system penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. In the multiple ascending dose part of first time in human Study 207187, clinically relevant preferred terms from the system organ class nervous system were experienced by 5 participants (somnolence, disturbance in attention, and lethargy) and showed that the greatest incidence arose in the GSK3640254 200 mg arms (Cohorts 5 and 7), but no dose/AE relationship was apparent. Seven participants experienced five psychiatric AEs: agitation, abnormal dreams, insomnia, depressed mood, and nightmare. All events were mild in intensity and considered by the investigator to be unrelated to study drug, apart from one participant from the 320 mg arm who experienced lethargy which was considered related to study drug.	will be included given no positive (abnormal) response. • Participants will undergo physical examinations and laboratory testing. In addition, participants will undergo continuous evaluation for AEs during their participation in the study; there are individual clinical stopping criteria and monitoring based upon incidence and intensity of treatment-emergent psychiatric AEs. Participants will be housed during key aspects of the study to ensure rapid diagnosis and management of any potential event. The C-SSRS will be administered during and after the treatment phase of the study. In case of positive (abnormal) response confirmed by the investigator, the participant will undergo immediate clinical assessment of suicidality (by the investigator or a consulting psychiatrist). Emergence of new onset suicidal ideation or a Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management. Guidance for the investigator on the management of emergent psychiatric symptoms will be available.
Rash	Across clinical trials, AEs leading to discontinuation have included urticaria and maculopapular rash.	• Participants will undergo continuous evaluation for adverse events during their participation in the trial supplemented by the use of physical exams. • Protocol includes individual participant stopping criteria, including: • Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement • Any allergic or hypersensitivity reactions • (see Section 7.1 for complete list of stopping criteria)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Radiolabelled Investigational Product: [^{14}C]-GSK3640254		
Radioactivity exposure risk ([^{14}C]-GSK3640254)	The total effective dose associated with IV and oral administrations of [^{14}C]-GSK3640254 is <1 mSv. The Period 1 dose is a microdose for which the associated radioactivity is less than the International Commission on Radiological Protection (ICRP, 1992) recommended threshold for clinical research projects with intermediate level of societal benefit. It is below the level identified as trivial risk by the ICRP, 1992 and below the maximum exposure threshold for the level of risk that is within variations of natural background radiation according to the World Health Organization (WHO, 1977) See Appendix 6.	In Period 2, participants will be monitored for recovery of radioactivity.
Study Procedures		
Local extravasation of intravenous microdose at the infusion site	GSK3640254 has not previously been administered by IV infusion in humans. In preclinical studies, no irritancy at site of injection was reported.	Usual IV care will include flushing the IV before administration of the dose and monitoring for correct positioning of the IV. Participants will be monitored for signs of pain at the injection site.
Entero-tracker for bile collection	Streaks of blood on the string due to local irritation have been infrequently noted. Gagging upon retrieval of the string can occur. On a few occasions, an entire string has been swallowed without ill effects and passes out from the body in the feces.	The string will be securely taped in place (to the cheek of each individual) during the collection time to minimise risk of swallowing the entire string.

2.3.2. Benefit Assessment

The healthy participants will receive no clinical benefit for participation in this study.

2.3.3. Overall Benefit: Risk Conclusion

Overall, the available data from non-clinical and clinical studies have not identified prohibitive risks associated with GSK3640254 at the exposures planned for this study. While there are a number of important potential risks identified for GSK3640254 and the study procedures, these can be addressed in this clinical trial with proper participant selection, close safety monitoring, and specific risk characterisation and mitigation.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine parent GSK3640254 and total drug-related radioactivity systemic concentrations following a single IV microtracer dose of [14C]-GSK3640254 (with an oral dose of non-radiolabelled GSK3640254) and oral dose of [14C]-GSK3640254[1]	• AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of parent and total drug-related material (radioactivity) in plasma and blood. • Volume of distribution at steady state (Vss) and clearance (CL) of parent after IV dose (Period 1 only). • Renal clearance of parent (CLr) after both IV and oral dose • Oral clearance (CL/F) and apparent volume of distribution (Vz/F) for the parent following oral administration
• To calculate the absolute oral bioavailability of GSK3640254	• Direct estimation of absolute oral bioavailability (F), indirect calculation of fraction of drug escaping first pass hepatic clearance (Fh), fraction absorbed (Fa) and fraction of drug escaping gut metabolism (Fg)
• To determine the rate and extent of excretion of total radioactivity in urine and feces and the total recovery of radioactivity, following IV and oral administration of [14C]-GSK3640254	• Urinary and fecal cumulative excretion as a percentage of the total radioactive dose
Secondary	
• To evaluate the safety and tolerability of GSK3640254 after single IV and oral doses in healthy participants.	• Characterize observed adverse events, and abnormal laboratory, 12-lead ECG, and vital signs assessments observed.
• To determine the blood:plasma ratio of [14C]-GSK3640254-related materials (total radioactivity) associated with blood cellular components	• Blood:plasma ratio of [^{14}C]-GSK3640254-related materials (total radioactivity)

Exploratory	
• To generate samples that will be used to characterize the metabolite profile of GSK3640254 following a single IV microtracer dose of [14C]-GSK3640254 with an oral dose of non-radiolabelled GSK3640254 (plasma, urine, feces, duodenal bile) and a single, oral dose of [14C]-GSK3640254 (plasma, urine and feces, duodenal bile).	• Characterization and quantification of metabolites in plasma, urine, feces, and duodenal bile (qualitative identification in bile). These analytical investigations will be conducted, and the results reported under a separate GSK nonclinical protocol.
• To evaluate the PK and relative bioavailability of GSK3640254 following administration of the 85 mg suspension compared to the 200 mg tablet	• AUC(0-inf), AUC(0-t) and Cmax

AUC(0–inf): Area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinite time, AUC(0–t): Area under the plasma concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments, Cmax: Maximum observed plasma concentration, tmax: time of occurrence of Cmax, t1/2: terminal phase half-life.

[1] For measured concentrations of GSK3640254 in plasma, the nomenclature **[^{14}C]-GSK3640254** describes the parent GSK3640254 concentration derived via analysis by liquid chromatography (LC) + AMS, whereas **GSK3640254** describes the parent GSK3640254 concentration derived via liquid chromatography-tandem mass spectrometry (LC-MS/MS).

4. STUDY DESIGN

4.1. Overall Design

This is a single group, single center, [^{14}C]-GSK3640254 mass balance study with a two-period, single sequence, and no masking.

This open-label, single-center, non-randomised, 2-period, single-sequence, mass balance study will enroll a cohort of 6 healthy male participants. The aim of the study is to assess the pharmacokinetics, balance/excretion, and metabolism of GSK3640254 using [^{14}C]-radiolabelled drug substance administered as an IV infusion of a microtracer dose with an oral tablet, non-radiolabelled dose (Treatment period 1) and a [^{14}C]-radiolabelled drug substance administered orally (Treatment Period 2).

Four to six healthy participants are deemed sufficient. To minimise the number of exposed to radiation, participants who discontinue early will not be replaced unless the total number of participants who complete dosing and all critical assessments drops below 4.

Each participant will be involved in the study for up to 10 weeks. He will have a screening visit, two treatment periods (Treatment Periods 1 and 2), separated by a washout period of at least 13 days between oral doses, and a follow-up visit 7 – 14 days after the last assessment in Treatment Period 2. During both treatment periods, participants will reside in the unit from the morning of Day -1 until all procedures are completed at 168 h post-dose (on Day 8). Participants may be asked to stay for up to 1 week longer in Treatment Period 2, if excretion of drug-related material takes longer than anticipated (see Figure 1).

Safety data will include AE reporting, 12-lead ECG, vital signs, and laboratory safety tests. Blood will be sampled extensively on the day of dosing and daily until Day 8, for assessing the PK of GSK3640254 and metabolites.

4.1.1. Screening Period

Participants must be screened within 30 days before the first dose of GSK3640254 and must meet all eligibility criteria.

Treatment Period 1 (oral tablets and ^{14}C-intravenous infusion)

On Day 1 of Treatment Period 1, after an overnight fast of at least 8 h, each participant will take a single 200 mg oral dose (2 x 100 mg tablets) of GSK3640254 with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat); the IV infusion of 100 µg of [^{14}C]-GSK3640254 (approximately 3.7 kBq; 100 nCi) will begin 5 h after oral dose and continue over 1 h. Blood samples, all voided urine, and feces will be collected continuously from Day 1 through Day 8, while duodenal bile will be collected as described below. Participants will be discharged on study Day 8 after completion of the 168-h sample collection and other planned assessments and instructed to return to the clinic on Day -1 of Treatment Period 2.

A non-invasive device (Entero-tracker) to collect duodenal bile will be used in Treatment Period 1. The bile string will be swallowed 2 h after the oral dose and 3 h before the IV infusion starts, a duration recommended to allow transit of the string to the duodenum. Participants will fast from insertion of the bile string until the completion of the IV infusion, at which point a food cue (small standard high-fat meal) will be given to stimulate gall bladder emptying. The Entero-tracker will be removed about 1.5 h after the IV infusion stops (7.5 h after the oral dose).

4.1.2. Treatment Period 2 (^{14}C-oral suspension)

On Day 1 of Treatment Period 2, after an overnight fast of at least 8 h, each participant will receive approximately 85 mg [^{14}C]-GSK3640254 (approximately 3.15 MBq; 85 µCi) as an oral suspension with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat). A non-invasive device (Entero-tracker) to collect duodenal bile will be used in Treatment Period 2. The Entero-tracker will be swallowed 2 h after oral dose. At 5.5 h after the start of oral dose, a food cue (small standard high-fat meal) will be given to stimulate gall bladder emptying. The collection bile string will be removed 1.5 h post the food cue (7 h after the oral dose) to capture the duodenal bile samples expelled from the gall bladder.

Blood, urine and fecal samples will be collected continuously from Day 1 through Day 8. Radioactivity quantification using liquid scintillation counting (LSC) will be performed on each 24-h urine collection and each 24-h fecal homogenate. Criteria for discharge for Period 2 are based on demonstrated cumulative recovery of radioactivity as outlined in Section 4.1.3. The inpatient stay may be extended by up to 7 days to meet the discharge criteria. In the unlikely event that excretion is still >1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect fecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

4.1.3. Demonstration of radioactivity recovery before discharge (Period 2)

LSC radio-quantification results from samples collected for Days 1 through 6 (through 144 h post-dose) will be reviewed on Day 8. The GlaxoSmithKline (GSK) In vitro / In vivo Translation (IV/IVT) Study Monitor should be consulted to agree with release of a participant. This process is outlined in detail in the Study Reference Manual (SRM).

- If >90% of the administered radioactivity has been recovered from the Day 1-6 samples, then the participant may be discharged on Day 8 after all scheduled assessments have been completed, including complete collection of Day 7 urine and feces samples (24 h collection period ending on Day 8).

- If ≤90% has been recovered, then the radio-quantification results will be re-evaluated on Day 9 with Day 7 results included.

On Day 9, if >90% has been recovered or <1% of the dose has been excreted on both Day 6 (120-144 h) and Day 7 (144-168 h), then the participant may be discharged on Day 9.

If the participant is not eligible for discharge on Day 9, or if the results are inconclusive, the participant will remain at the unit. Urine and fecal collections will continue at 24-h intervals for up to 7 additional days (until the morning of Day 15). Once <1% of the dose is recovered in 2 consecutive 24-h periods where samples are provided (and the samples were of sufficient size to make this assessment), or once >90% of the radioactivity has been recovered, the participant will be discharged.

All remaining participants will be discharged from the unit no later than Day 15. In the unlikely event that excretion is still ≥1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect fecal samples only, at home, over 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

4.1.4. Follow-up

Follow-up procedures will be done 7-14 days after the participant's last assessment in Treatment Period 2. The follow-up period may be extended if:

(i) radioactivity excretion is still higher than 1%;

(ii) a participant has an unresolved AE at the follow-up visit, which, in the opinion of the investigator, merits further follow-up; or

(iii) new information becomes available that supports an extended follow-up period.

The investigator and GSK IV/IVT Monitor and/or GSK Medical Monitor as appropriate will agree on the nature of the extended follow-up. For example, participants may have a telephone follow-up at which they are asked about AEs, or participants may be asked to attend extra outpatient visits for additional monitoring of plasma radioactivity levels and/or for extra safety tests. The extra safety tests might include tests that are not described in this protocol. The investigator reserves the right, during or after the study, to repeat safety tests or to do any extra safety tests that are in the best interest of the participants. Those extra tests may or may not be described in this protocol.

4.2. Scientific Rationale for Study Design

In the first treatment period of this study, an IV microtracer dose of [^{14}C]-GSK3640254 will be infused over 1 h, beginning 5 h after an oral dose of non-radiolabelled GSK3640254 (tablets). The non-radiolabelled 200 mg dose of GSK3640254 is to ensure that the PK of the microdose represents a therapeutically relevant total body exposure to the drug. In the second treatment period, an 85 mg oral suspension of [^{14}C]-GSK3640254 will be used for comparison.

Biliary elimination pathways will be characterised after the IV and oral doses by inclusion of duodenal bile collection in both Treatment Periods 1 and 2. Complexities in human fecal sample analysis such as extraction, stability in the gastrointestinal tract, and endogenous contamination are minimised through assessment of the metabolite profile in duodenal bile after IV drug administration.

In order to characterize potential biliary elimination pathways, this study will also employ the Entero-Tracker for sampling of duodenal bile to conduct qualitative assessment of drug metabolites in this matrix. The Entero-Tracker is based on a similar device, Entero-Test which has been shown to be an easy-to-use and minimally-invasive method for sampling bile from the duodenum (Guiney, 2011). The Entero-Tracker is a recent replacement device for Entero-Test that is an Food and Drug Administration (FDA) 510k exempt device. Information on the biliary disposition of drug-related material derived in the current study may avoid the need for invasive methods of bile collection in future studies

Details of blood, bile, urine and fecal sample collection and processing, storage and shipping procedures are detailed in the SRM.

4.3. Justification for Dose

Based on modelling and simulation of virology and PK data, coupled with an ongoing proof of concept (POC) study for GSK3640254 (208132) in HIV-infected participants, the currently projected therapeutic dose range to be investigated in Phase IIb is 50-200 mg once daily. The population PK model of GSK3640254, including parameter uncertainty, was integrated with the PK/Pharmacodynamic (PD) model of GSK3532795 and the distribution of protein binding adjusted (PBA) EC90 values obtained with GSK3640254 from an in vitro experiment with 36 Gag/PR genotyped viruses (e.g. mean of 19.1 ng/mL with CV% of 33%). Further details of the findings in this study are provided in the IB.

The 100 µg microtracer dose administered as a 1 h IV infusion in Treatment period 1 is projected (based on allometry and a conservative assumption of 15% oral bioavailability) to achieve a GSK3640254 Cmax ~3 ng/mL, which is >200-fold lower than the geometric mean Cmax following a single 200 mg dose in healthy participants (Study 207187) and >400 fold lower than the geometric mean Cmax following a single 200 mg dose in HIV-infected patients. This dose can be categorised as a microdose and as such the required safety cover is detailed in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3 (R2) (International Conference on Harmonisation, 2009.) In Treatment Period 2, the ^{14}C labelled solution dose of GSK3640254 is 85 mg (85 uCi) which is partly based on practical limitations and is well within the target dose range to be evaluated in Phase IIb studies.

Preclinical toxicology species provide safety cover for systemic exposure to GSK3640254. Predicted steady-state exposures for a projected 200 mg QD maximum dose in Phase IIb 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 GI intolerability and minimal effects of parietal cells following 4 weeks of dosing. However, in this single dose design absorption, distribution, metabolism, and excretion (ADME) study of very limited drug exposure these findings become less relevant.

In vitro studies using hepatocytes from nonclinical species and humans show that there is generally no qualitative difference in metabolites formed. Preliminary non-radiolabelled

studies showed that GSK3640254 was the predominant drug-related component with low levels of oxidative metabolites in human plasma following repeat oral doses of 320 mg/day (see IB, Section 1.1).

4.3.1. GSK3640254 Oral Dose (Treatment Periods 1 and 2)

The oral GSK3640254 dose is within the therapeutic range for the treatment of HIV. The 200 mg dose is lower than the highest once-daily dose (320 mg QD) in the first time in human (FTIH) study 207187. In Study 207187 (single Ascending Dose [SAD]/ multiple Ascending Dose [MAD]), doses up to 200 mg QD for 14 days were well tolerated.

4.3.2. GSK3640254 Intravenous Dose (Treatment Period 1)

The dose of [^{14}C]-GSK3640254 to be administered intravenously is a microdose of 100 μg, which will be infused over 1 h. A microdose was selected because GSK3640254 has not previously been administered by IV infusion to humans. That dose level meets the criterion for a microdose, for the following reasons:

- It is ≤ 100 μg.
- It is ≤ 1/100th of the lowest predicted pharmacologically-active oral dose in HIV-patients (i.e., 5 mg single, oral dose) based on a PK/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%).
- Predicted steady-state exposures for a higher 200 mg QD dose are essentially equal to the NOAEL exposure in a 4-week oral toxicity study in rats, although no NOAEL was identified in dogs for GI 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 lowest-observed-adverse-effect level (LOAEL) exposures, the lowest exposures where minimal, reversible effects on parietal and/or chief cells were identified.

To ensure clinically-relevant systemic exposure during the microdose, the IV infusion of [^{14}C]-GSK3640254 will be administered with an oral non-radiolabelled dose of 200 mg GSK3640254.

The 100 μg microtracer dose administered as a 1-h IV infusion is projected (based on allometry) to achieve a GSK3640254 Cmax ~3 ng/mL, which is >200-fold lower than the lowest observed geometric mean human Cmax following a 200 mg dose (Study 207187). This dose can be categorised as a microdose and as such required safety cover is detailed in ICH M3 (R2).

4.3.3. Radiolabel Dose

The effective dose of radiolabelled drug administered in human mass balance studies is calculated from data on the distribution and elimination of the radioactive drug from laboratory animals, considering the nature of the isotope, the route of administration, the

concentration of radioactivity in individual tissues/organs and the residence or elimination half-life of the radioactivity from those tissues/organs.

4.3.4. Total Radiation Exposure

In this study, each participant will receive the following doses of radioactivity:

- approximately 3.7 kBq (100 nCi) in Treatment Period 1.
- approximately 3.15 MBq; (85 µCi) in Treatment Period 2.

The total amount of radiation exposure in the study is ~3.15 MBq; (~85.1 µCi).

It is estimated that the combined total effective dose for the two treatment periods will be <1 mSv. On this basis, the maximum administered activity would comply with the ICRP, 1992 recommendation of a 1 mSv maximum for Category IIa projects (0.1 – 1 mSv ; minor risk), further details are in Appendix 6.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study including the follow-up visit (end of study visit).

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age
1. Participant must be 30 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics
2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and ECG. A participant with a clinical abnormality or laboratory parameter (i.e. outside the reference range for the population being studied), which is not specifically listed in the eligibility criteria, may be included only if the investigator agrees and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
3. History of regular bowel movements (averaging one or more bowel movements per day).
4. Non-smoker, or ex-smoker who hasn't regularly smoked for the 6 months before screening.

Weight
5. Body weight of 50 kg and above, and body mass index (BMI) within the range 19.0 to 31.0 kg/m^2 (inclusive).

Sex
6. Male only. Male participants are eligible to participate if they agree to the following during the study, including washout periods: • Refrain from donating sperm • And Either: 1) be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain

abstinent OR 2) Agree to use a male condom when having penile-vaginal intercourse with a woman of childbearing potential unless vasectomised.

Informed Consent
7. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions
1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Participants with a history of cholecystectomy must be excluded.
2. Significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention ; or interfering with the interpretation of data.
3. Any clinically relevant abnormality identified at the screening medical assessment (physical examination/medical history) clinical laboratory tests, or 12-lead ECG.
4. Current episode, recent history, or chronic history of diarrhoea.
5. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
6. 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.
7. 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 VH/GSK Medical

Monitor.

8. 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
9. Regular use of known drugs of abuse or history of drug abuse or dependence within 6 months of the study.
10. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >21 units. One unit is equivalent to 8 g of alcohol: a glass (~240 mL) of beer, 1 small glass (~100 mL) of wine or 1 (~25 mL) measure of spirits.
11. History of or regular use of tobacco- or nicotine-containing products in the 3 months prior to screening.
12. Medical history of cardiac arrhythmias, prior myocardial infarction in the past 3 months, or cardiac disease or a family or personal history of long QT syndrome.
13. QTcF >450 msec

    NOTES:

    The QTc must be the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

    For purposes of data analysis, QTcF will be used as specified in the Reporting and Analysis Plan (RAP).
14. At Screening or prior to the first dose, a supine blood pressure (BP) that is persistently higher than 140/90 mmHg.
15. At Screening or prior to the first dose, a supine mean heart rate (HR) outside the range of 50–100 bpm. A heart rate from 100 to 110 bpm can be rechecked by electrocardiogram or vital signs within 30 minutes to verify eligibility.
16. A participant with known or suspected active COVID-19 infection OR contact with an individual with known COVID-19, within 14 days of study enrollment (WHO definitions Section 10.9.3.2)

Prior / Concomitant Therapy

17. Past or intended use of over-the-counter or prescription medication, including analgesics (eg, paracetamol), herbal medications, or grapefruit and Seville orange juices within 14 days prior to the first dose of study intervention until completion of the follow-up visit unless approved by the Investigator in conjunction with a ViiV Healthcare (VH)/GSK Medical monitor.
18. Treatment with any vaccine within 30 days prior to receiving study intervention.

Prior / Concurrent Clinical Study Experience
19. Current enrolment in a clinical trial; recent participation in a clinical trial and has received an investigational product within 3 months before the first dose in the current study. 20. Exposure to more than 4 new chemical entities within 12 months before the first dose in the current study. 21. Participation in a clinical trial involving administration of ^{14}C-labelled compound(s) within the last 12 months. A participant's previous effective dose will be reviewed by the medical investigator to ensure there is no risk of contamination/carryover into the current study. 22. Received a total body radiation dose of greater than 10.0 mSv (upper limit of IRCP category II) or exposure to significant radiation (e.g., serial x-ray or computed tomography [CT] scans, barium meal, etc.) in the 3 years before this study.

Diagnostics Assessments
23. Alanine transaminase (ALT) ≥1.5x upper limit of normal (ULN). A single repeat of ALT is allowed within a single Screening period to determine eligibility. 24. Bilirubin ≥1.5xULN (isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). A single repeat of any laboratory abnormality is allowed within a single Screening period to determine eligibility. 25. Presence of Hepatitis B surface antigen (HBsAg) at screening or positive Hepatitis C antibody test result at screening or within 3 months before the first dose of study intervention AND positive on reflex to hepatitis C ribonucleic acid (RNA). 26. Positive HIV-1 and -2 antigen/antibody immunoassay at Screening. 27. Any positive (abnormal) response confirmed by the investigator or qualified designee-administered C-SSRS. 28. Any Grade 2 to 4 laboratory abnormality at Screening, with the exception of creatine phosphokinase (CPK) and lipid abnormalities (e.g., total cholesterol, triglycerides), and ALT (described above), will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any laboratory abnormality (other than a viral screening test for HIV-1/2, hepatitis B Virus [HBV], or hepatitis C Virus [HCV]) is allowed within a single Screening period to determine eligibility. 29. Any significant arrhythmia or ECG finding (e.g., prior myocardial infarction in the past 3 months, symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained or sustained ventricular tachycardia, second-degree atrioventricular block Mobitz Type II, third-degree atrioventricular block, complete heart block, orconduction abnormality) which, in the opinion of the investigator or VH/GSK Medical Monitor, will interfere with the safety for the individual

participant. Any acute laboratory abnormality at Screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
OTHER EXCLUSIONS
30. Has had an occupation which requires monitoring for radiation exposure, nuclear medicine procedures, or excessive x-rays within the past 3 years. 31. Loss of more than 400 mL blood during the 3 months before screening, eg as a blood donor, or plan to donate blood or blood products in the 3 months after the end of the trial. 32. Unwillingness or inability to follow the procedures outlines in the protocol, including the use of the string bile collection device. 33. History of sensitivity to GSK3640254, or their components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

In both Treatment Periods, participants will be required to take their oral dose of GSK3640254 with a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat). The meal will be given 30 minutes before dosing and must be consumed within 25 minutes.

In Treatment Period 1, participants will be required to fast from insertion of the bile string until the completion of the IV infusion, a period of approximately 4 hours. In Treatment Period 2, participants will also be required to fast from insertion of the bile string until 5.5 hours post dose.

In both treatment periods at the times defined in the SoA a standard, small high-fat meal will be provided. Meal times are specified in both treatment periods for Day 1, on all other days, meals will be served at the standard times of the clinical site.

Participants will refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or their fruit juices from 7 days before the start of study intervention until the follow-up visit.

During the inpatient stays, participants will refrain from consumption of nuts and seeds, or other foods that may cause issues with homogenization of feces. Peas must not be consumed from Day -1 until 48 hours after each oral dose in both treatment periods (to avoid potential complications with retrieval of the steel ball from the bile string device prior to sample homogenization).

No water is allowed until 2 h after oral dosing (apart from rinsing the oral suspension dose of [^{14}C]-GSK3640254); water is allowed *ad libitum* at all other times.

Adequate hydration should be encouraged to help facilitate stool sample production. If needed, participants may consume prunes or prune juice to facilitate stool samples.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from alcohol for 24 h before the screening visit until the follow-up visit.

Participants must not be current smokers (no smoking for at least 6 months before the screening visit). Use of tobacco- or nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be allowed from screening until after the final follow-up visit.

5.3.3. Activity

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

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol (see Table 4).

6.1. Study Intervention(s) Administered

Detailed instructions for dosing will be provided in the SRM.

Table 4 Treatments administered during the study

Study Intervention Name:	[^{14}C]-GSK3640254 IV Solution-for-Infusion	[^{14}C]-GSK3640254 Oral Powder-in-Bottle	GSK3640254 Oral Tablet
Dosage formulation:	IV solution	Powder-in-bottle	Oral tablet
Treatment Period	1	2	1
Unit dose strengths:	Strength: 10 µg/mL Dosage Level: 100 µg	Strength: 85 mg Dosage Level: 85 mg	Strength: 2 x 100 mg tablet Dosage Level: 200 mg
Route of Administration:	IV infusion	Oral	Oral
Dosing instructions:	Administer 10 mL intravenously over 1 h.	Administer total 85 mg dose (reconstituted into a suspension using 25 mL vehicle just before dosing) with meal in the morning.	Two tablets taken with meal in the morning with 240 mL of room temperature water
Manufacturer:	Drug product: Hammersmith Medicines Research (HMR)	Drug product: HMR	GSK Ware, UK
Physical Description:	A clear, colourless solution free from visible particulates	White powder (white to slightly coloured for the reconstituted suspension)	White, round shaped, film coated tablets containing no markings

6.2. Preparation/Handling/Storage/Accountability

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

A description of the methods and materials required for preparation of [^{14}C]-GSK3640254 solutions for IV infusion and oral administration is provided in the Technical Agreement (TA). A Quality Agreement will be in place with the contract research organization (CRO) performing the manufacturing operations.

Further guidance and information for the final disposition of unused study intervention are provided in the TA.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

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

Dose administrators must follow site-specific procedures for handling radiolabelled GSK3640254.

6.3. Measures to Minimize Bias: Randomization and Blinding

- This is an open-label study with no randomization and no blinding of participants, site personnel, or sponsor personnel.
- Eligibility will be established during the Screening Period. A cohort of six participants will be admitted to the clinical research unit on the same day and will complete Period 1 and Period 2 on the same schedule with the same study interventions. This approach minimizes potential bias associated with temporal effects.

6.4. Study Intervention Compliance

Individual doses will be prepared for each participant from a bulk supply and will be confirmed by a second member of the study site staff.

All participants will receive their doses 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 and reported in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. For oral doses, study site personnel will examine each participant's mouth to ensure that the study intervention was ingested. For IV doses, administration will be documented in the source documents and reported in the CRF.

6.5. 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 must be discontinued by 15 days before the start of the study intervention. These 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.

Participants must abstain from taking prescription and non-prescription drugs (including vitamins and dietary and herbal supplements) within 14 days before the start of study intervention until completion of the follow-up visit unless approved by the Investigator in conjunction with a VH/GSK Medical monitor.

Special warnings and precautions for use of GSK3640254 are given in the IB, Section 6.

6.6. Dose Modification

No dose modification is allowed.

6.7. Intervention after the End of the Study

Participants will not receive any additional study intervention from GSK after completion of the study because only healthy participants are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

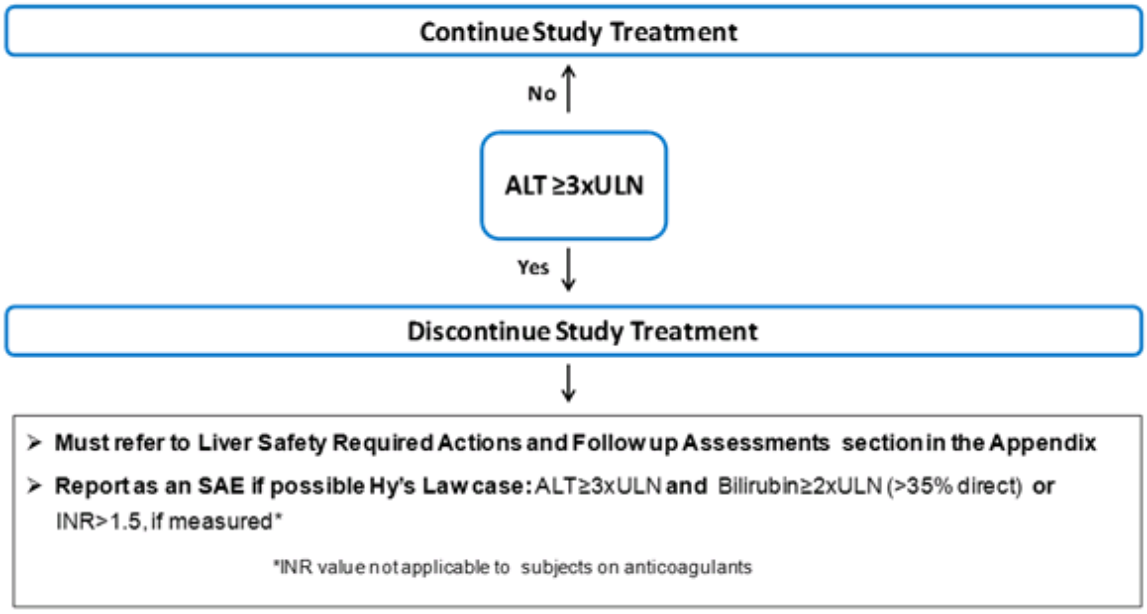
7.1. Discontinuation of Study Intervention

7.1.1. Liver Chemistry Stopping Criteria

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

Study intervention will be discontinued and be discontinued from the study for a participant if liver chemistry stopping criteria are met:

Figure 2 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

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

7.1.2. QTc Stopping Criteria

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

- The ECG taken on Day –1 of each treatment period will be a single reading to confirm eligibility. In each study period, the Day 1 pre-dose timepoint will have triplicate averaged QTcF (over a brief approximately 5 to 10 minute recording

period). This pre-dose triplicate averaged QTcF value will serve as the baseline for each applicable study period.

- An enrolled participant that develops an on-treatment QTcF >500 ms or an increase from Baseline QTcF >60 ms should have two repeat unscheduled ECGs within 10 minutes. Using these triplicate ECGs, if the average QTcF>500 ms or an increase from Baseline QTcF >60 ms, the participant will be withdrawn from the study. Finally, this participant should have repeated unscheduled ECGs until their QTcF measurement returns to their original averaged QTcF value at Day 1 pre-dose.

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

7.1.3. Individual Participant Laboratory Abnormality and AE Stopping Criteria

A participant must permanently discontinue study intervention and be discontinued from the study for the pre-specified reasons below. Please refer to Section 8.2.5 and Section 8.2.6 for details on suicidal risk and GI toxicity monitoring, respectively.

- Severe pain, redness, bleeding or swelling at the infusion site.
- Liver chemistry abnormalities exceeding the threshold criteria (see Section 7.1.1).
- QTc result meeting the stopping criteria (see Section 7.1.2)
- SAE considered related to study intervention
- Any clinically significant AE deemed to require discontinuation of study intervention
- Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement
- Any allergic or hypersensitivity reactions to either formulation
- Any Grade 3 or higher psychiatric AE
- New onset suicidal ideation
- Any Grade 3 or higher AE related to study intervention
- Any Grade 4 AE or laboratory abnormalities (with the exception of an asymptomatic Grade 4 cholesterol, CPK, or triglyceride)

7.1.4. Columbia-Suicide Severity Rating Scale Criteria

Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered C-SSRS during the treatment phase of the study, the participant will undergo immediate clinical assessment of suicidality (by the investigator or a consulting psychiatrist). Emergence of new onset suicidal ideation or a

Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management.

Refer to the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed. See Section 8.2.5 for more details.

7.1.5. COVID-19

A participant must permanently discontinue study intervention and be discontinued from the study if they have COVID infection as clinically determined by the investigator (suspect, probable, or confirmed using the most recent version of the WHO case definition) or by laboratory testing.

7.1.6. Other study stopping criteria

The study will be halted if there is a SAE or 2 severe AEs, considered to be related to the investigational medicinal product (IMP). If following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the Medicines and Healthcare Regulatory Authority (MHRA) and Research Ethics Committee (REC). The trial will not restart until the amendment has been approved by the MHRA and REC.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. If study intervention is permanently discontinued, the participant will remain in the study for confirmation of excretion of radioactivity (see Section 4.1.3). Participants who withdraw from the study early should undergo an early withdrawal visit as defined in the SoA.

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 may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The investigator will record in the source documents the results of follow-up examination of withdrawn participants, if the participant gives their consent.

In the event of vomiting directly after oral dosing withdrawal may be considered. Refer to Section 8.5.4 for details.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he 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 will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- 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 GSK Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing the ICF may be utilized for screening purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The timing and number of planned study assessments, including safety, and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this 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.
- 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 600 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Efficacy of GSK3640254 as a treatment for HIV or any other indication is not assessed in this study.

8.2. Safety Assessments

Safety assessments include AEs, SAEs, ECGs, vital signs, and clinical laboratory tests. Planned time points for all safety assessments are provided in the SoA.

Baseline is defined as the value for clinical laboratory, ECG, VS, and physical exam results that is collected closest to but before the first dose on Day 1 in each Treatment Period.

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the eyes, skin, joints, and the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded, and BMI calculated and recorded.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will also be measured and recorded.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Blood pressure, pulse, respiratory rate and temperature will be assessed.
- Vital signs will be measured in a resting position after 5 minutes rest. Single measurements will be obtained for all parameters. Repeats can be obtained if the original reading cannot be interpreted.
- 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.

8.2.3. Electrocardiograms

- ECG measurements will be obtained as outlined in the SoA. Full 12 lead ECGs will be recorded with the participant in a resting position after 5 minutes rest. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcF will be calculated (machine read or manually).
- At each time point at which ECGs are required, single ECG measurements are appropriate with the exception of the following: a) Day 1 pre-dose ECGs for each treatment period will be performed in triplicate and b) two additional ECGs are required if the initial ECG measurement indicates prolonged QTc (i.e., QTcF >500 msec) using the automated or manually calculated QTcF value. The average QTcF value of all three ECGs will be used to determine eligibility.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2: Clinical Laboratory Tests 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.
- All laboratory tests with values considered clinically-significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or GSK Medical Monitor.
- If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2: Clinical Laboratory Tests must be conducted in accordance with the local laboratory manual and the SoA.

8.2.5. Suicidal Risk Monitoring and Management of Emergent Psychiatric Symptoms

GSK3640254 is not a central nervous system active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with previous MI GSK3532795, all participants will undergo screening using the C-SSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator, will exclude them from participating. A repeat assessment will be done during the treatment phase of the study. In case of positive (abnormal) response confirmed by the investigator, the participant will undergo immediate clinical assessment of suicidality (by the investigator or a consulting psychiatrist). Emergence of new onset suicidal ideation or a Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management.

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia-Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment.

Emergent non-suicidal psychiatric AE evaluation and management:

- Any Grade 1 or 2 psychiatric AE: A Grade 1 or 2 psychiatric AE may result in additional unscheduled visits (in-clinic or at home) as clinically indicated. This may include a more in-depth assessment of AE through interview, additional unscheduled clinical labs, and/or imaging. Psychiatric consultation may be required at the discretion of the investigator. Any pharmacotherapy should be discussed with the medical monitor.
- Any Grade 3 or 4 psychiatric AE: As described in Section 7.1.3, 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).

8.2.6. Gastrointestinal Toxicity Evaluation and Monitoring Plan

Preclinical toxicology studies in rats and dogs have suggested a potential for GI-related toxicity with GSK3640254. This section provides general guidance to the investigator on the evaluation and management of primarily upper GI symptoms (Table 5). The investigator may contact the VH/GSK Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the study.

Table 5 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.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

As described in Section 10.4, intensity of AEs (and lab abnormalities) will be graded using the division of acquired immunodeficiency syndrome (DAIDS) Grading table.

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

See Section 10.9.3.2 for the assessment and capture of AEs and SAEs related to COVID-19.

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

- All SAEs will be collected from the signing of the informed consent form start of study intervention until the follow-up visit at the time points specified in the SoA.
- All AEs will be collected from start of study intervention until the follow-up visit at the time points specified in the SoA.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including a

death, at any time after a participant has been discharged from the study, and he considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until the participant's final visit.

- If a pregnancy is reported, the investigator should inform GSK within 24 h of learning of the pregnancy and should follow the procedures outlined in Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, any dose of GSK3640254 greater than 700 mg within a 24-hour period will be considered an overdose.

GSK does not recommend specific treatment for an overdose as there is no specific antidote for GSK3640254. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the investigator should:

1. Contact the GSK Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities as agreed with the Medical Monitor on a case-by-case basis.

3. Obtain a plasma sample for PK analysis 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 discontinuation will be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetics will be assessed in whole blood, plasma, urine, and faeces. Samples collected as part of this study for metabolite profiling will be analysed under a separate non-clinical protocol. The results of those analyses will be reported separately.

8.5.1. Plasma Sample Collection

Blood samples will be collected at timepoints specified in the SoA for measurement of each of the following:

- blood and plasma total radioactivity
- plasma [^{14}C]-GSK3640254
- plasma concentrations of GSK3640254
- plasma metabolite profiling.

The actual date and time of each blood sample collection will be recorded.

Details of PK blood sample collection, including the volumes to be collected, processing, storage and shipping procedures are provided in the SRM.

Samples will be stored for no longer than 15 years after the end of the trial.

8.5.2. Urine Sample Collection

Urine samples will be collected over the time periods specified in the SoA. Urine samples will be used to determine total radioactivity excreted in urine and for subsequent metabolite profiling (to be analysed under a separate protocol).

All participants will be asked to void their bladders before study intervention administration. A blank (pre-dose) urine sample will be collected pre-dose (up to 3.5 h before oral dosing) in Treatment Periods 1 and 2. After oral dosing, in each Treatment Period, urine will be collected over 24 h collection periods as follows: 0-24 h, 24-48 h, 48 – 72 h, 72 – 96 h, 96 – 120 h, 120-144 h, 144-168 h. Further details of urine sample collection, processing, storage and shipping procedures are provided in the SRM.

8.5.3. Fecal Sample Collection

Fecal samples will be collected over the time periods specified in the SoA. Fecal samples will be used to determine total radioactivity excreted in feces and for subsequent metabolite profiling (to be conducted in a separate study). A fecal sample will be collected from each participant before dosing in Treatment Periods 1 and 2 (the pre-dose sample can be collected up to 48 h before oral dosing). After oral dosing, in each Treatment Period, faeces will be collected over 24 h collection periods as follows: 0-24 h, 24 – 48 h, 48 – 72 h, 72 – 96 h, 96 – 120 h, 120-144 h, 144-168 h. Further details of fecal sample collection, processing, storage and shipping procedures are provided in the SRM.

8.5.4. Vomitus collection (if occurs)

Any episodes of vomiting should be recorded in the CRF as an adverse event.

If a participant vomits within the first 4 h after oral dosing, the participant will be considered unsuitable for evaluation and will be withdrawn from the study. Even if withdrawn, participants should remain in the clinic and samples collected until the discharge criteria outlined in Section 4.1.3 are met. Should the participant vomit after the first 4 h post oral dosing, the participant will not be withdrawn.

If a participant vomits any time during or after IV dosing, the participant will not be withdrawn.

As practical, the vomitus will be collected and the amount of radioactivity present in the vomitus estimated, using the sample handling procedure described for quantifying radioactivity in stools. During dosing, staff should ensure that each participant has a suitable pre-weighed plastic collection vessel available for that purpose.

8.5.5. Bile Sample Collection

Bile samples will be collected via a non-invasive string device (Entero-tracker) in both Treatment Periods 1 and 2, as specified in the SoA. The samples obtained will be used to investigate potential biliary metabolites in a separate GSK study.

The string device comprises a gelatine capsule which contains either 90 cm or 140 cm of nylon string attached to a small steel weight. One end of the string is attached to the outside of the mouth before swallowing the capsule, so that it can be retrieved at the end of the bile collection procedure. The gelatine capsule dissolves in the stomach whilst the string and weight continue to the duodenum via peristalsis.

In Treatment Period 1, the bile string will be swallowed at approximately 2 h post oral dose and 3 h before the IV infusion starts, a duration recommended to allow transit of the string to the duodenum. At 6 h post oral dose and upon completion of the IV infusion, a small moderate fat meal acting as a food cue will be used to stimulate gall bladder emptying. The bile string will be removed about 1.5 h after the IV infusion stops (7.5 h after the oral dose).

In Treatment Period 2, the bile string will be swallowed at 2 h post oral dose. A food cue will be used to stimulate gall bladder emptying at 5.5 h after the oral dose, and the string will be withdrawn 7 h post dose.

On withdrawal of the string through the mouth the steel weight separates from the string at the pyloric sphincter and is excreted in the feces. Once the string has been removed from the participant it will be frozen and shipped for metabolite profiling (to be conducted in a separate study). Full details of the bile sample collection, processing, storage and shipping procedures are provided in the SRM.

8.5.6. Sample Analysis

Total radioactivity measurements in urine samples and fecal homogenates will be determined by LSC and/or by AMS. Total radioactivity measurements from plasma derived from blood will be analysed, as appropriate, by AMS in Treatment Period 1 and by LSC and/or by AMS, for Treatment Period 2, as detailed in the SRM.

[^{14}C]-GSK3640254 and GSK3640254 plasma concentrations will be analysed, as appropriate, as detailed in the SRM.

Aliquots of plasma, urine, fecal homogenates and duodenal bile will be provided for metabolite analysis. Metabolite analysis will be performed and reported separately, under a separate nonclinical GSK study.

Analysis of all samples (plasma, urine, feces, and duodenal bile) will be performed under the control of DMPK and Bioanalysis, Immunogenicity and Biomarkers (BIB), GSK, the details of which will be included in the SRM. Raw data will be archived at the bioanalytical site (detailed in the SRM).

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetic samples will not be taken in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessment

Immunogenicity will not be assessed in this study.

8.10. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

Final analyses will be performed after the completion of the study and final dataset authorization.

9.1. Statistical Hypotheses

This study is not designed for statistical testing and therefore has no formal statistical hypothesis.

9.2. Sample Size Determination

No formal sample size calculation has been performed for this study. However, the sample size reflects an accepted industry standard for human ADME studies using ^{14}C-radiolabelled drug. Additionally, the design of the study in terms of the concomitant administration of intravenous with oral administration (Period 1) inherently reduces variability in the parameters determined, versus a cross-over design for absolute bioavailability assessment, while enabling cross-over to Period 2 in the same participants.

The primary objective of the study is to gain a better understanding of the compound's pharmacokinetic, excretory, and metabolic profile and 4 to 6 participants are deemed sufficient for this purpose. Six participants will be enrolled into the study. To minimise the number of participants exposed to radiation, those participants that discontinue early will not be replaced unless the total number of participants who complete both Periods 1 and 2 drops below 4.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Screened Population	All participants who were screened for eligibility. This will be the population for reporting screened population data.
Safety Population	All participants who take at least 1 dose of study intervention. Participants will be analysed according to the treatment they received. This will be the population for reporting safety and study population data.
Pharmacokinetic Population	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).

9.4. Statistical Analyses

Details of the planned statistical reporting will be described in the RAP.

9.4.1. Efficacy Analyses

This is not applicable.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population. Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL). Further details will be given in the RAP.

9.4.3. Pharmacokinetic Analyses

Plasma GSK3640254 concentration-time data will be listed for each participant and summarised by treatment and planned sampling time. [^{14}C]-GSK3640254 and radioactivity concentrations in whole blood and plasma will be reported similarly. Individual participant, mean and median plasma GSK3640254, [^{14}C]-GSK3640254, and total radioactivity concentration–time profiles will be plotted for each treatment on both a linear and semi-log scale.

Pharmacokinetic analysis will be performed by or under the direct auspices of Clinical Pharmacology Modelling & Simulation, GSK. Plasma GSK3640254, [^{14}C]-GSK3640254, and total radioactivity concentration–time data will be analysed by non-compartmental methods with WinNonlin Version 6.3 or above. 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, for GSK3640254, [^{14}C]-GSK3640254, and total radioactivity (whole blood and plasma) as data permits: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), AUC(0–t) and AUC(0-inf), terminal phase rate constant (λ_z), and apparent terminal phase half-life ($t_{1/2}$) following oral and IV dosing. Additionally, Vss, CLr, and CL will be derived following IV dosing and CL/F and Vz/F will be derived following oral dosing. These parameters will be summarised descriptively.

Absolute bioavailability will be estimated for oral dose for each participant and will be summarized.

Derivation of the urine and fecal radioactivity parameters will be through support provided by CRO partners. The following radioactivity parameters will be determined from the urine and fecal radiolabelled drug-related material (total radioactivity) data, and will be listed and summarised by treatment:

- Percentage excreted in urine (Fe%[urine]) within each collection period and cumulative urinary recovery and fraction excreted over the total collection period.
- Percentage excreted in feces (Fe%[fecal]) with each collection period and cumulative fecal recovery and fraction excreted over the total collection period and cumulatively over the collection period.

- Total excretion (sum of urine and fecal excretion), Fe% [total] will be calculated by collection interval for each participant.

The urine, fecal and total radioactivity parameters will be listed, summarised and plotted, as appropriate.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. Production of the summaries, listings and figures of the plasma, urine and feces data will be performed under the direct auspices of Clinical Statistics, GSK.

Further details regarding the tables, figures and listings to be produced for the study report will be given in the RAP.

9.5. Metabolite profiling

The metabolic profiling/structural characterisation aspect of this work will be performed by GSK (or a GSK representative) and CRO partners in a separate nonclinical study and reported separately.

9.6. Interim Analyses

No interim analyses will be performed.

9.7. Other Analyses

Special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the main study SAP; alternatively, a separate SAP focussing on modified data handling rules and analyses may be prepared, taking into account applicable regulatory guidance and industry best practices for handling such situations [DHHS, 2020; EMA, 2020a; EMA, 2020b].

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) 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.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

- Participants must be informed that their participation is voluntary. 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.

10.1.4. Data Protection

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

10.1.5. 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 GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided

by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (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.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.1.7. Source Documents

- 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.
- 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.
- Definition of what constitutes source data can be found in the SRM.

10.1.8. Study and Site Closure

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

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

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

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

10.1.9. 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.

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- The requirement for fasting before laboratory sample collection will be determined by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count red blood cell (RBC) Count Hemoglobin Haematocrit	RBC Indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) Absolute and % Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Urea Creatinine Uric acid Fasting glucose Total cholesterol Low density lipoprotein (LDL) cholesterol, High density lipoprotein (HDL cholesterol) Triglycerides	Potassium Sodium Chloride Calcium Phosphate	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT), ALT/ Serum Glutamic-Pyruvic Transaminase (SGPT) Alkaline phosphatase	Total and direct bilirubin Total Protein Albumin Globulin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if leukocyte esterase, nitrites, blood or protein is abnormal)			
Screening only Tests	• Alcohol breath test, urine cotinine test • Carbon Monoxide (CO) breath test • Drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antigen/antibody immunoassay, HBsAg, and hepatitis C virus antibody with reflexive HCV RNA)			

NOTES:
[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 7. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
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. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
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, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 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.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by 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 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 (See Section 10.4).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the 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 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 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** 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 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 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 GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to 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 of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of each SAE being reported.
- 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 or SAE coordinator by

telephone. • Contacts for SAE reporting can be found in the SRM.
SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Correct Version 2.1, July 2017

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the hyperlink here to the U.S, 2017 Grading Table.

Alternatively, paste this into your browser:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.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.**

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

10.5.1. Collection of Pregnancy Information:

For male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

10.6. Appendix 6: An assessment of the radiation dose to male volunteers from the oral and IV administration of the study intervention

Public Health England

Protecting and improving the nation's health

OFFICIAL-SENSITIVE [COMMERCIAL] Contract Report

CRCE-RHE-23-2019

Assessment of the Radiation Dose to Male Volunteers from the Oral Administration of [^{14}C]GSK3640254 mesylate

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Approval: July 2019
Publication: July 2019
File Reference Number B340/913

ASSESSMENT OF THE RADIATION DOSE TO VOLUNTEERS FROM ADMINISTRATION OF [14C]-GSK3640254 MESYLATE

Contents

1. Introduction

GlaxoSmithKline have provided experimental data on the biokinetics of [^{14}C]GSK3640254 mesylate following its oral administration to pigmented and albino rats. The data have been used to determine the likely dose to male volunteers from a single administration of the radio-labelled compound. The assumption is made that the levels of uptake and retention by tissues will be the same in man as in the experimental animals. Committed equivalent doses to tissues and organs and committed effective dose (E(50)) have been calculated according to the 1990 Recommendations of the International Commission on Radiological Protection (ICRP)[1] as implemented in the Ionising Radiations Regulations 1999[2] in response to EU Council Directive 96/29/Euratom[3]. ICRP Publication 105[4] recommends the use of dose constraints, where the exposure of volunteers in biomedical research provides no direct benefit to them, to limit any inequity between individual risk and societal benefit and because there is no specific further protection in the form of a dose limit. The E(50) can be compared with the dose categories proposed for research projects involving human volunteers by the World Health Organization (WHO)[5] and ICRP[6].

2. Data used in calculations

Results were provided for the urinary and faecal excretion of ^{14}C following the oral administration of [^{14}C]GSK3640254 mesylate to albino rats. Expressed as percentages of total excretion, the values used for the calculations were 0.04% urinary and 99.96% faecal excretion.

Data were provided for the tissue distribution of ^{14}C after oral administration of [^{14}C]GSK3640254 mesylate to pigmented rats. Concentrations of radio-labelled compound retained in the tissues were expressed as nanogram equivalents per gram (ng eq/g) of tissue. These concentrations were converted to values for the percentage of administered activity retained in individual tissues or organs using standard organ weights[7]. Doses were calculated using values for 21 tissues at 5 time-points between 1 and 240 hours after administration. Retention half-time data were provided for the eye on the basis of measurements in pigmented rats; a half-time of 23.2 hours was estimated.

3. Method of calculation

The initial step is the calculation of the number of transformations (U) in each source region from 1 Bq of administered drug. These values were calculated for the period for which data were supplied by the trapezoidal method of integration. Any fraction of the ^{14}C remaining in tissues or organs at the last time point was assumed, conservatively, to be lost with a half-time of 100 days. This half-time was applied to residual activity in all tissues and organs except for the eye, for which the estimated value of 23.2 hours was used (see Section 2).

The values of U for the contents of the gut compartments, gall bladder and urinary bladder were calculated, as recommended by Dolphin and Eve[8], from the fraction of the administered activity passing through their contents and their mean residence time in each compartment. Calculations were made assuming that 100% of the faecally excreted activity was released into the gut in bile.

In order to calculate committed equivalent doses, $H_T(50)$ (Sv), to the target organs, the values of U are combined with a set of values known as Specific Effective Energies (SEEs)[9]. In short, the SEEs give the dose to each target region, T, per transformation in each source organ, S.

$$H_T(50) = \sum_S U(S,50) \times SEE(T,S)$$

The SEEs are calculated using data on absorbed fractions, (Φ) derived from a mathematical phantom[9], representing a reference adult male body, with additional data for the prostate taken from Stabin[10]. Absorbed fractions represent the fraction of energy emitted in each source that is absorbed in each target. In simple cases where S and T are the same, e.g. liver, the absorbed fraction for non-penetrating radiations is equal to one. The expression for SEE can be simply written

$$SEE(T,S) = \frac{\varepsilon}{m_T}$$

where ε is the mean energy of the emission (J) and m_T is the mass of the target organ (kg). The organ masses used for the calculations are those specified by the ICRP[11].

The committed effective dose, E(50), is the sum of the committed equivalent doses to individual tissues or organs, each weighted to allow for the relative contributions of tissues and organs to the total detriment; taking account of the probability of attributable fatal cancer, the weighted probability of attributable

non-fatal cancer, the weighted probability of severe hereditary effects and the relative length of life lost[1]. Thus:

$$E(50) = \sum_T w_T \cdot H_T(50)$$

where $H_T(50)$ is the committed equivalent dose in tissue or organ T and w_T is the tissue weighting factor.

Weighting factors are specified for testes (0.2); colon, lung, red bone marrow and stomach (each 0.12); bladder, breast, liver, oesophagus and thyroid (each 0.05) and bone surfaces and skin (each 0.01)[1]. A complication is that the current dosimetric model of the gastrointestinal tract does not consider doses to the oesophagus, and divides the colon into upper and lower large intestine[12]. Until a revised model is available, doses to the oesophagus have been calculated using the thymus data (this is a standard dosimetric procedure justified for penetrating photon radiation on the basis of the proximity of the oesophagus and thymus). The dose to the colon is taken to be the mass weighted mean of the doses to the upper large intestine and lower large intestine. Doses from ^{14}C in transit through the gut were calculated separately from doses from activity retained in the gut wall. The dose received by bone surfaces was calculated using data for retention in bone marrow, assuming uniform distribution of activity throughout marrow. Where information is not provided for retention in soft tissues with specific tissue weighting factors, but information is provided for retention in muscle tissue, the equivalent dose to muscle is assumed to apply; in this case, for the breasts. The mass weighted average of the dose to remainder tissues is given a total weighting factor of 0.05 unless any one tissue exceeds the highest equivalent dose to named tissues when it is attributed a weighting factor of 0.025; the weighting factor for the remainder becomes 0.025.

4. Results

The results of the calculation of committed effective dose, E(50), from the oral administration of [^{14}C]GSK3640254 mesylate, based on the animal data supplied, are given in Table 1. The E(50) is the sum of the weighted equivalent doses to named tissues and the remainder tissues. The E(50) to a male volunteer following the oral administration of [^{14}C]GSK3640254 mesylate was calculated as 2.9×10^{-10} Sv Bq^{-1}. The doses to the colon and testes contribute 66% and 23% of the E(50), respectively.

5. Conclusions

The E(50) value obtained for oral administration of [^{14}C]GSK3640254 mesylate to male volunteers was 2.9 x 10^{-10} Sv Bq^{-1} (Table 1). On this basis, the maximum administered activity that would comply with the WHO[5] recommendation of a 0.5 mSv maximum for Category 1 projects (see Table 2) would be 1.7 MBq (46 µCi). To comply with the ICRP[6] Category 1 limit of 0.1 mSv (see Table 2), the maximum activity would be 0.34 MBq (9.2 µCi).

ASSESSMENT OF THE RADIATION DOSE TO VOLUNTEERS FROM ADMINISTRATION OF [14C]-GSK3640254 MESYLATE

6. Table 1

Estimated radiation doses to human tissues after oral administration of [^{14}C]GSK3640254 mesylate (Based on animal data)

Tissues	w_T	Equivalent Dose (Sv Bq^{-1})	Equivalent Dose x w_T (Sv Bq^{-1})	Contribution to effective dose (%)
Testes	0.2	3.40E-10	6.79E-11	23.17
Red bone marrow	0.12	1.04E-11	1.25E-12	0.43
Colon	0.12	1.61E-09	1.93E-10	65.92
Lungs	0.12	3.40E-12	4.08E-13	0.14
Stomach	0.12	2.04E-10	2.45E-11	8.36
Urinary Bladder	0.05	9.50E-14	4.75E-15	0.00
Breasts	0.05	1.02E-11	5.12E-13	0.17
Liver	0.05	2.40E-11	1.20E-12	0.41
Oesophagus	0.05	5.79E-11	2.90E-12	0.99
Thyroid	0.05	1.84E-12	9.20E-14	0.03
Skin	0.01	5.08E-11	5.08E-13	0.17
Bone surfaces	0.01	5.18E-12	5.18E-14	0.02
Remainder	0.05	1.14E-11	5.69E-13	0.19
Highest remainder tissue	0.00	0.00E+00	0.00E+00	0.00
Effective dose			**2.93E-10**	100.00
	Mass (g)		**Equivalent Dose x Mass**	
Adrenals	14	1.37E-11	1.91E-10	
Brain	1450	2.71E-12	3.92E-09	
Eyes (pigmented region)	1.5	7.13E-12	1.07E-11	
Heart	330	3.33E-12	1.10E-09	
Kidneys	310	1.92E-11	5.96E-09	
Muscle	29000	1.02E-11	2.97E-07	
Pancreas	140	2.43E-11	3.40E-09	
Pituitary	0.6	2.68E-11	1.61E-11	
Prostate	17	3.68E-11	6.26E-10	
Spleen	150	9.19E-12	1.38E-09	
Small intestine	650	5.63E-11	3.66E-08	
Gall bladder	10	1.38E-09	1.38E-08	
Thymus	25	4.64E-11	1.16E-09	

Category 1 Limits:	WHO 1977 <0.5 mSv	**1.7 MBq (46 µCi)**
	ICRP 1992 <0.1 mSv	**0.34 MBq (9.2 µCi)**

9

ASSESSMENT OF THE RADIATION DOSE TO VOLUNTEERS FROM ADMINISTRATION OF [14C]-GSK3640254 MESYLATE

7. Table 2

Categories of risk and corresponding level of benefit for human exposure in biomedical research

WHO 1977

Category	Effective dose equivalent	Level of risk
I	Less than 0.5 mSv	Within variations of natural background
II	More than 0.5 mSv but less than 5 mSv	Within dose limits for members of the public
III	More than 5 mSv but less than 50 mSv	Within dose limits for persons occupationally exposed to radiation

ICRP 1992

Level of risk	Risk category	Corresponding effective dose range (adults) (mSv)	Level of societal benefit
Trivial	Category I ($\approx 10^{-6}$ or less)	<0.1	Minor
Minor to intermediate	Category II IIa ($\approx 10^{-5}$) IIb ($\approx 10^{-4}$)	0.1 - 1 1 – 10	Intermediate to moderate
Moderate	Category III ($\approx 10^{-3}$ or greater)	>10	Substantial

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

Phase I Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology.

These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance.

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

Table 7 Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 h
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 h
• Monitor participants twice weekly until liver</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)[4]
• Serum 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</td></tr>
</table>

chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

[1] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

[2] All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) 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] Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

[4] Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention. Sample handling and shipping instructions are in the SRM.

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ADME	Absorption, distribution, metabolism, and excretion
ALT	Alanine aminotransferase
AMS	Accelerator Mass Spectrometry
AST	Aspartate Aminotransferase
AUC(0–inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0–t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
BIB	Bioanalysis, Immunogenicity and Biomarkers
BMI	Body mass index
BP	Blood Pressure
bpm	Beats per minute
Bq	Becquerel
CA	Capsid
C_{max}	Maximum observed concentration
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CL/F	Oral clearance
CLr	Renal clearance
cm	Centimeter
CO	Carbon Monoxide
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations (US)
CMV	Cytomegalovirus
CPK	Creatine phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
DAIDS	Division of AIDS
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
F	Absolute bioavailability
Fa	Fraction absorbed
FDA	Food and Drug Administration

Fh	Fraction of drug escaping first pass hepatic clearanc
Fg	Fraction of drug escaping gut metabolism
FTIH	First time in human
Gag	Group-specific antigen
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HBC	Hepatitis C Virus
HDL	High density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IVIVT	In vitro / In vivo Translation - Investigative Safety & Drug Metabolism, GSK
kDa	Kilodalton
kg	Kilograms
kg/m^2	Kilograms per meter square
LC	Liquid Chromatography
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOAEL	Lowest-observed-adverse-effect level
LSC	Liquid Scintillation Counting
LFTs	Liver Function Tests
MBq	Megabecquerel
MCH	Mean corpuscular hemoglobin
MCV	mean corpuscular volume

mSv	Millisievert
µCi	Micro Curie
µg	Microgram
µSv	Microsievert
MAD	Multiple Ascending Dose
mg	Milligrams
MHRA	Medicines and Healthcare Regulatory Authority
MI	Maturation Inhibitor
mL	Millilitre
mmHg	Millimeters of mercury
ms	Milliseconds
MSDS	Material Safety Data Sheet
mSv	Millisievert
nCi	Nano Curie
ng	Nanograms
NOAEL	No Observed Adverse Effect Level
PBA	Protein binding adjusted
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
POC	Proof of concept
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
QTL	Quality tolerance limit
RNA	Ribonucleic acid
RAP	Reporting and Analysis Plan
RBC	Red blood cell
REC	Research Ethics Committee
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SGPT	Serum Glutamic-Pyruvic Transaminase
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SoA	Schedule of Activities
SPI	Spacer peptide 1
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA	Technical Agreement
t_{max}	Time of occurrence of C_{max}
t½	Terminal phase half-life
TQT	Thorough QT
UK	United Kingdom

ULN	Upper Limit of Normal
VH	ViiV Healthcare group of companies
Vss	Volume of distribution at steady state
Vz/F	Apparent volume of distribution
WHO	World Health Organisation
λz	Lambda-z (Terminal Phase Rate Constant)

Trademark Information

Trademarks of ViiV Healthcare
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10.9. Appendix 9: COVID-19 Pandemic and Clinical Trial Continuity

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

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

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

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

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

10.9.1. Changes to Study Visits and Study Procedures

- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

10.9.2. COVID-19 Experimental Agents

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

The protocol does not allow for concurrent enrolment in other interventional studies, though, there may be exceptions in this pandemic. If a participant is being considered for enrolment into clinical studies for COVID-19 treatment or vaccinations, please reach out to the Medical Monitor who will discuss with the study team (to include Safety Review Team and input from the PK Scientist/Clinical Pharmacologist) who will consider relevant drug interactions and to ensure that continued study participation remains appropriate.

10.9.3. COVID-19 Specific Data Capture

10.9.3.1. Capturing COVID-19 Specific Protocol Deviations

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

10.9.3.2. Capturing COVID-19 Specific AEs and SAEs

ViiV Healthcare are monitoring the evolving situation with respect to COVID-19 carefully and the impact this may have on ongoing or planned clinical trials. It is important for the study team to describe COVID-19 related adverse events/serious adverse events and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.
2. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve; the most recent definitions should be consulted for each case (WHO). When reporting both serious and non- serious adverse events (related to COVID-19 infection), investigators should use the following Verbatim terms:

    a) Suspected COVID-19 infection; or
    b) Probable COVID-19 infection; or
    c) Confirmed COVID-19 infection

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

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

10.9.3.2.1. WHO Case Definition (March 20, 2020 Version):

Suspected case:

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

OR

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

OR

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

Probable case:

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

OR

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

Confirmed case:

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

COVID-19 Contact:

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

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

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

10.10. Protocol Amendment History

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

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