TITLE PAGE

Protocol Title: Effects of GSK3640254 on the Single-Dose Pharmacokinetics of Probe Substrates (Caffeine, Metoprolol, Montelukast, Flurbiprofen, Omeprazole, Midazolam, Digoxin, and Pravastatin) in Healthy Subjects

Protocol Number: 213052 Amendment-2

Compound Number or Name: GSK3640254

Study Phase: Phase 1

Short Title: Evaluation of the One-way Pharmacokinetic Interaction Between GSK3640254 and Caffeine, Metoprolol, Montelukast, Flurbiprofen, Omeprazole, Midazolam, Digoxin, and Pravastatin in Healthy Adults

Sponsor Name and Legal Registered Address:

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

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

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

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SPONSOR SIGNATORY:

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Date

The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in SRM.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	*12-Apr-2021*	*TMF-12140653*
Amendment 1	*02-Jun-2020*	*2019N422949_01*
Original Protocol	*25-Feb-2020*	*2019N422949_00*

Amendment 2: XX-APR-2021

Overall Rationale for the Amendment: The primary driver for the protocol amendment was to remove the analysis of Pravastatin Lactone.

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Objectives & Endpoints	Removed Pravastatin Lactone from secondary endpoint	Not performing analysis
3 Objectives & Endpoints	Removed Pravastatin Lactone from secondary endpoint	Not performing analysis
8.5 Pharmacokinetics	Removed Pravastatin Lactone from described analysis plan	Not performing analysis
9.4.1 Pharmacokinetics Analysis	Removed Pravastatin Lactone from described analysis plan	Not performing analysis

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Effects of GSK3640254 on the Single-Dose Pharmacokinetics of Probe Substrates (Caffeine, Metoprolol, Montelukast, Flurbiprofen, Omeprazole, Midazolam, Digoxin, and Pravastatin) in Healthy Subjects

Short Title: Evaluation of the One-way Pharmacokinetic Interaction Between GSK3640254 and Caffeine, Metoprolol, Montelukast, Flurbiprofen, Omeprazole, Midazolam, Digoxin, and Pravastatin in Healthy Adults

Rationale: The current study is being conducted to investigate the potential drug-drug interactions when GSK3640254 is co-administered with a cocktail of cytochrome P450 and transporter probe substrates in healthy participants. This study will aid in understanding these interactions and resulting changes in exposure (if any) when drugs that are metabolized via these pathways are given in combination with GSK3640254.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of GSK3640254 on the PK of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin under fed conditions in healthy participants	AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin
Secondary	
• To assess the safety and tolerability of GSK3640254 alone and in combination with caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin in healthy participants	• Safety and tolerability parameters for adverse events/serious adverse events, observed and change from baseline clinical laboratory assessments, electrocardiograms, and vital sign measurements
• To characterize the steady-state PK of GSK3640254 in the presence of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin in healthy participants	• AUC(0-t), AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 for GSK3640254
• To characterize the single-dose PK of the metabolites for the probe substrate drugs (α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, and 1-hydroxymidazolam)	• AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for metabolites, and metabolite-to-parent ratios for Cmax and AUC(0-∞)

AUC(0-τ) = area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the plasma concentration-time curve from time zero to time t; Cτ = plasma concentration at the end of the dosing interval; Cmax = maximum observed concentration; PK = pharmacokinetics; Tmax = time of maximum observed concentration; t1/2 = apparent terminal phase half-life.

Overall Design: This is an open-label, single-sequence, one-way drug interaction study to investigate the effect of GSK3640254 200 mg on the pharmacokinetics (PK) of a metabolic probe cocktail containing the substrate drugs caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg.

The study will consist of a screening period and 3 sequential treatment regimens. Participants will be screened within 28 days before the first dose of study intervention.

There will be a washout of 10 days between dosing of Regimen 1 and initiation of Regimen 2. There is no planned washout between Regimen 2 and Regimen 3. The participants will fast overnight for at least 8 hours prior to dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Pharmacokinetic blood samples for analysis of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin (and metabolites) will be obtained pre-dose and up to 120 hours after Regimen 1 and Regimen 3 dosing. Pharmacokinetic blood samples for analysis of GSK3640254 will be obtained pre-dose on Days 17 to 20 during Regimen 2, and pre-dose and up to 120 hours after Regimen 3 dosing.

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

Study assessments will be performed as indicated in the Schedule of Activities. Participants will be confined to the clinic from check-in (Day –1) until discharge on Day 26.

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

Number of Participants: Approximately 20 participants will be treated to ensure that 18 evaluable participants complete the study.

Intervention Groups and Duration:

- Treatment A: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg on Day 1 (Regimen 1)
- Treatment B: GSK3640254 200 mg once daily on Days 11 to 20 (Regimen 2)
- Treatment C: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg co-administered with GSK3640254 200 mg on Day 21 (Regimen 3)

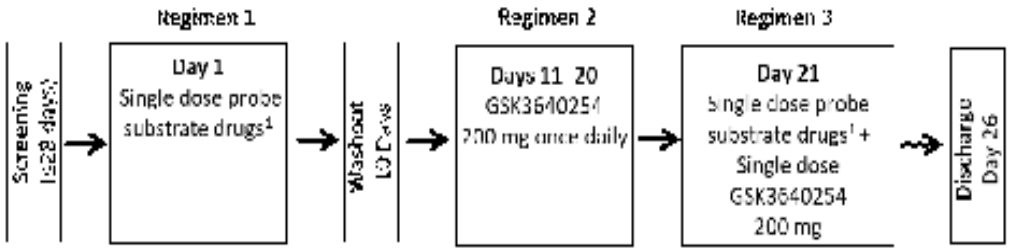
The duration of the study, including Screening, is approximately 54 days.

Data Monitoring or Other Committee: No.

1.2. Schema

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

Figure 1 Study Design Schematic



1. Probe substrate drugs: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg

1.3. Schedule of Activities (SoA)

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

Screening Visit

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

HIV = human immunodeficiency virus.

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

Time and Events Table

Procedure		Regimen 1 Treatment A (Day 1) Washout (Days 2-10)					Regimen 2 Treatment B		Regimen 3 Treatment C						Notes
	Check-in Day –1	Day 1	Day 2-5	Day 6	Days 7-9	Day 10	Days 11-19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	
Admit to clinic	X														
Discharge from clinic														X	
Brief physical examination	X							X					X		Includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
Vital sign measurements	X	X	D2			X	D11, D14, and D17	X	X	X	X	X	X	X	Blood pressure and pulse measured in triplicate at pre-dose on Days 1, 11, and 21. Respiratory rate measured pre-dose and post-dose every 15 minutes for the first 2 hours and every 30 minutes for the subsequent 2 hours on Days 1 and 21 (may be monitored longer if indicated by clinical condition).
Temperature check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulse oximetry		X							X						Continuous pulse oximetry measured pre-dose and through 4 hours after dosing on Days 1 and 21 (may be monitored longer if indicated by clinical condition).
Twelve-lead ECG	X	X	D2, D3, and D5			X	D11	X	X	X	X		X		ECGs on Days 1, 11, and 21, will be taken pre-dose, and at 2 and 4 hours post-dose. Pre-dose ECGs on Days 1, 11, and 21 will be taken in triplicate.

Procedure		Regimen 1 Treatment A (Day 1) Washout (Days 2-10)					Regimen 2 Treatment B		Regimen 3 Treatment C						Notes
	Check-in Day –1	**Day 1**	**Day 2-5**	**Day 6**	**Days 7-9**	**Day 10**	**Days 11-19**	**Day 20**	**Day 21**	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	
Drug, alcohol, and cotinine screen	X														See Appendix 2 for tests.
Laboratory assessments (hematology, chemistry, urinalysis)	X		D2 and D5			X	D15	X		X			X		See Appendix 2 for tests.
Pregnancy test	X												X		
Columbia-Suicide Severity Rating Scale						X		X		X			X		
Study intervention: probe substrate drugs		X							X						See Section 6.1 for study intervention details.
Study intervention: GSK3640254 200 mg							X	X	X						See Section 6.1 for study intervention details.
Probe substrate drug PK sampling		Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours post-dose.							Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours post-dose						
GSK3640254 PK sampling							Pre-dose on Days 17, 18, 19, 20 and 21. Post Day 21 dose at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, 96, and 120 hours.								
AE review		←==========→													
SAE review	←==========→														
Concomitant medication review	←==========→														

Abbreviations: AE = adverse event; D = day; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event.

- Participants will fast overnight for at least 8 hours prior to dosing and will receive the moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Refer to Section 5.3.1 for meal timings.
- Evaluations scheduled for Day 25 will also be performed for participants who discontinue prior to completing Day 26, including PK samples for GSK3640254 and probe substrate drugs.
- The Institutional Review Board/Independent Ethics Committee will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form. The changes will be approved by the health authority and the ethics committee before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is an open-label, single-sequence, one-way drug interaction study to investigate the effect of GSK3640254 200 mg on the pharmacokinetics (PK) of a metabolic probe cocktail of substrate drugs containing caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg. This study will aid in understanding these interactions and resulting changes in exposure (if any) when given in combination with GSK3640254.

2.2. Background

GSK3640254 is a human immunodeficiency virus (HIV) maturation inhibitor (MI) which is improved over prior developmental MIs in the following ways: (1) it exhibits significantly improved pan-genotypic coverage and potency against polymorphic variants; (2) *in vitro* data suggest that GSK3640254 exhibits a higher barrier to emergence of resistant viruses (except for A364V); (3) GSK3640254 has improved potency *in vitro* toward all HIV-1 subtypes; and (4) it has a projected lower once daily (QD) human dose. Summaries of the pre-clinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GSK Document Number 2018N379610_01].

2.2.1. Summary of GSK3640254 Clinical Pharmacokinetics

Pharmacokinetic data for clinical studies performed to date are summarized as follows:

- Following multiple-dose administration over 50 to 320 mg dose range for 14 days with a moderate fat meal in the single ascending dose (SAD)/multiple ascending dose (MAD) first time in human (FTIH) Study 207187:
    - Median time of maximum observed concentration (Tmax) ranged between 3.8 to 4.3 hours.
    - The mean half-life ranged from approximately 22 to 29 hours.
    - There was a slightly less than dose-proportional increase in maximum observed concentration (Cmax) and area under the plasma concentration-time curve (AUC) from time zero to the end of the dosing interval at steady state (AUC[0-τ]) from 50 to 320 mg QD.
    - The exposure on Day 14 was, on average, 1.9- to 2.3-fold higher for Cmax and 2.2- to 2.6-fold higher for AUC(0-τ) compared to those on Day 1.
    - PK variability (between-subject variability) ranged from 8% to 50%.
- There was no clinically meaningful drug interaction between GSK3640254 and either tenofovir alafenamide/emtricitabine (Study 208134) or dolutegravir (Study 209712).

- Using a population PK model, a comparison of Phase 1 SAD/MAD (Study 207187) and Phase 2a proof of concept (Study 208132) showed the PK in HIV-1 infected subjects was similar to that in healthy volunteers.

Additional information regarding clinical PK data can be found in the CIB [GSK Document Number 2018N379610_01].

2.2.2. Summary of GSK3640254 Metabolism

With recombinant cytochrome P450 (CYP) enzymes, GSK3640254 was mainly metabolized by CYP3A4/3A5, CYP2C9, CYP1A2 and CYP2C8. GSK3640254 was stable in recombinant uridine diphosphate glucuronosyltransferase (UGT) enzymes. In rat and dog plasma, GSK3640254 was either the only or the predominant drug-related component with minor oxidative metabolites (e.g., hydroxylation and N-dealkylation). Preliminary analysis of bile samples of bile duct cannulated rats dosed with unlabeled GSK3640254 suggested that GSK3640254 was eliminated mainly by direct glucuronidation followed by biliary excretion in rats. In human plasma, GSK3640254 was the predominant drug-related component with low levels of oxidative metabolites as shown by preliminary human metabolism study following repeat oral doses of 320 mg/day. Additional information regarding GSK3640254 metabolism can be found in the CIB [GSK Document Number 2018N379610_01

2.2.3. Summary of GSK3640254 Safety

A summary of safety data from the clinical studies performed to date is summarized below:

- No deaths or treatment-related serious adverse events (SAEs) have been reported during clinical studies with GSK3640254.

- The majority of adverse events (AEs) were mild (Grade 1).

- Treatment-related AEs leading to study discontinuation included maculopapular rash (Study 207187 [SAD/MAD]) and urticaria (Study 208134 [drug-drug interaction (DDI) with tenofovir alafenamide/emtricitabine]).

- Clinically notable AEs of elevated transaminases occurred in Studies 207187 (SAD/MAD, n = 1 healthy volunteer) and 208135 (DDI with oral contraceptive Portia [ethinyl estradiol/levonorgestrel], n = 8 healthy volunteers). Subsequent analysis in Study 208135 showed no PK/pharmacodynamic relationship with either GSK3640254 or Portia (ethinyl estradiol/levonorgestrel) and elevated transaminases.

- Treatment-related AEs reported in more than 1 study included headache (Studies 207187, 208131, and 208132) and nausea (Studies 207187 and 208132).

- With the exception of elevated transaminases as noted above, across studies there were generally no clinically significant changes in vital sign measurements, electrocardiogram (ECG) results, or safety laboratory parameters.

The full safety profile for GSK3640254 can be found in the CIB [GSK Document Number 2018N379610_01].

2.2.3.1. Cardiac Safety

A cardiodynamic evaluation of healthy participants in the MAD portion of Study 207187 [GSK Document Number 2020N430256_00] (placebo or GSK3640254 dose range 50 to 320 mg daily for 14 days) was performed. Serial ECGs were extracted from continuous Holter monitors at time-matched baseline on Day –1 and for approximately 24 hours post-dose on Days 1 and 14. There were no abnormal clinically significant arrhythmias or QT prolongations (values >500 ms or increases >60 ms from baseline) observed for any participant in the SAD or MAD cohorts. In the concentration-corrected QT interval (QTc) analysis, a final model with a treatment effect-specific intercept reasonably represented the data. The slope of the concentration-QTc relationship was 0.004 ms per ng/mL (90% CI: 0.0023 to 0.0048) with a small treatment effect-specific intercept of -0.9 ms (90% CI: -4.47 to 2.69). The QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTc using the Fridericia formula (QTcF) effect above 10 ms could be excluded in GSK3640254 plasma concentrations of up to approximately 2000 ng/mL (corresponding to doses approximately ≤ 200 mg QD; note, the dose used in the current study will be 200 mg QD).

2.2.4. Probe Substrate Drugs

GSK3640254 is primarily metabolized by CYP3A4/3A5, CYP2C9, CYP1A2, and CYP2C8. Co-administration of CYP inhibitors could, therefore, affect the metabolism and/or elimination of GSK3640254. The probe substrate cocktail for CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, P-glycoprotein (P-gp), and organic anion-transporting polypeptide (OATP)1B1 has been tested and no evidence of mutual PK interaction between the cocktail drugs was found [Tye, 2016; Garimella, 2018]. Therefore, it is unlikely that the probe cocktail will impact the PK of GSK3640254.

2.2.4.1. Caffeine

Caffeine was chosen as a substrate for CYP1A2. Following oral administration, caffeine is rapidly and nearly completely absorbed from the gastrointestinal (GI) tract. An oral dose of caffeine of 1 mg/kg (equivalent to a cup of coffee) produces a Cmax of 1 to 2 mg/L. The dose used in this study (200 mg; i.e., approximately 3 mg/kg) is equivalent to about 2 cups of coffee. The mean Tmax for caffeine is 1 hour (range 0.5 to 1.5 hours). The mean apparent terminal phase half-life (t1/2) for caffeine is 5.4 hours (range 2.3 to 13.9 hours). The main route of elimination is via formation of 1,7-dimethylxanthine (paraxanthine) by demethylation which is catalysedby CYP1A2 [Newton, 1981; Tangh-Liu, 1983]. Participants will take 2 single doses of 200 mg caffeine administered 21 days apart in this study. Caffeine is contraindicated in participants who have demonstrated hypersensitivity to any of its components. Potential AEs, although not likely to be seen with this dose, include GI irritation, central nervous system stimulation, and increases in systolic and diastolic blood pressure and heart rate [Vivarin, 2014] prescribing information].

2.2.4.2. Metoprolol

Metoprolol was chosen as a substrate for CYP2D6. Metoprolol is a selective β_1-adrenoreceptor blocking agent and is used as an antihypertensive agent either alone or in combination with thiazide-type diuretics. Metoprolol is highly metabolized with less than 5% excreted in urine as unchanged drug with the rest being metabolites. Metoprolol is metabolized by CYP2D6 and; therefore, poor metabolizers have several-fold higher concentrations than extensive metabolizers. This causes a difference in the t1/2 of metoprolol: approximately 7 to 9 hours in poor metabolizers and 3 to 4 hours in extensive metabolizers. However, the CYP2D6-dependent metabolism has little effect on safety or tolerability of the drug. The Tmax occurs approximately 1.5 hours after dosing. Metoprolol is metabolized into at least 4 metabolites: α-hydroxylation (mediated by CYP2D6) into α-hydroxymetoprolol; O-demethylation into O-demethylmetoprolol, and subsequent oxidation into metoprolol acid; and by deamination into deaminated metoprolol. Doses in patients are 100 to 450 mg per day. Asthmatic patients should not take beta blockers. Contraindications for metoprolol are generally related to cardiac conditions (which are excluded for this healthy participant study). Other contraindications include hypersensitivity to metoprolol and related derivatives or to any of the excipients or other beta-blockers. Potential AEs include tiredness, dizziness, shortness of breath, bradycardia, palpitations, wheezing and dyspnea, diarrhea, nausea, dry mouth, gastric pain, constipation, flatulence, and hypersensitivity reactions (pruritus or rash) [Metoprolol tartrate prescribing information, 2013]. In this study, participants will receive only 2 single doses of 100 mg metoprolol administered 21 days apart, decreasing the probability of the aforementioned risks.

2.2.4.3. Montelukast

Montelukast was chosen as a substrate for CYP2C8. Montelukast is a prescription medication used to treat patients with asthma and allergic rhinitis. Montelukast is rapidly absorbed following oral administration and has an absolute oral bioavailability of 64%. Peak plasma concentrations occur approximately 3 to 4 hours after dosing. The t1/2 is 2.7 to 5.5 hours. Montelukast is extensively metabolized to one major oxidative metabolite (M6) (36-hydroxymontelukast) via CYP2C8 (and CYP2C9, although minor) and several minor metabolites that are mainly excreted into the bile. Montelukast is contraindicated in patients who are hypersensitive to it or any of its components. Potential AEs include upper respiratory infection, fever, headache, abdominal pain, and diarrhea [Singulair prescribing information, 2019]. Dosing in patients is usually 10 mg daily; in this study, participants will take 2 single doses of 10 mg montelukast administered 21 days apart, decreasing the probability of the aforementioned risks.

2.2.4.4. Flurbiprofen

Flurbiprofen was chosen as a substrate for CYP2C9. Flurbiprofen is a chiral, nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities, likely through prostaglandin synthetase inhibition. Flurbiprofen is metabolized via CYP2C9 to several hydroxylated metabolites with the major metabolite being 4-hydroxy-flurbiprofen which is not known to have any anti-inflammatory activity. Approximately 70% of the administered dose is excreted in the urine with only 3% of the dose excreted as unchanged drug. The Tmax occurs at approximately 1.9 hours. The t1/2

of both enantiomers are similar, being approximately 4.7 and 5.7 hours for the *R*- and *S*-enantiomers, respectively. The primary concern with NSAIDs is GI bleeding or irritation. Contraindications include a history of asthma (excluded for this healthy participant study), urticaria, or allergic-type reactions after taking aspirin or other NSAIDs, or hypersensitivity to any component of the product [Flurbiprofen prescribing information, 2009]. The highest recommended starting dose in patients is 100 mg given several times a day; participants in this study will receive only 2 single doses of 100 mg flurbiprofen administered 21 days apart, decreasing the probability of the aforementioned risks.

2.2.4.5. Omeprazole

Omeprazole was chosen as a substrate for CYP2C19. Omeprazole is a proton pump (H+, K+-ATPase) inhibitor used as a blocker of gastric acid secretion in gastric parietal cells. Omeprazole is extensively metabolized to the primary metabolites 5-hydroxyomeprazole (mediated by CYP2C19) and omeprazole sulfone. The Tmax is approximately 0.5 to 3.5 hours after oral administration. The mean t1/2 is 0.5 to 1 hour. Hypersensitivity to substituted benzimidazoles or to any component of the formulation is a contraindication. Overdosage is associated with central nervous system symptoms (headache) and GI symptoms (abdominal pain, nausea, diarrhea, vomiting, and flatulence) [Omeprazole prescribing information, 2015]. While patients receive 20 to 60 mg per day, participants in this study will receive only 2 single doses of 40 mg omeprazole administered 21 days apart, decreasing the probability of the aforementioned risks.

2.2.4.6. Midazolam

Midazolam was chosen as a substrate for CYP3A4. Midazolam is an ultra-short acting benzodiazepine used clinically for brief sedation. After oral administration, midazolam is almost completely absorbed from the GI tract. The mean t1/2 of midazolam and 1-hydroxymidazolam, its major metabolite (mediated by CYP3A4), are about 3 hours in humans. The Cmax is reached at about 1 hour after oral administration. Midazolam is contraindicated in patients with a known hypersensitivity to the drug or allergies to cherries or formulation excipients. Potential AEs may include transient drowsiness, nausea and emesis, and respiratory depression [Allonen, 1981; Midazolam hydrochloride syrup prescribing information, 2012]. Participants in this study will receive 2 single doses of 5 mg midazolam administered 21 days apart, decreasing the probability of the aforementioned risks.

2.2.4.7. Digoxin

Digoxin was chosen as a substrate for P-gp. Digoxin is indicated for the treatment of mild to moderate heart failure and for rate control in chronic atrial fibrillation. Following oral administration, Cmax of digoxin occurs between 1 and 3 hours. Oral absorption of digoxin tablets is between 60% and 80%. In healthy participants with normal renal function, t1/2 is 1.5 to 2 days; therefore, steady-state concentrations are not achieved until approximately 10 days. When given after a meal, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations

usually constitutes a contraindication to digoxin. Because digoxin slows sinoatrial and atrioventricular conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete atrioventricular block. Common adverse reactions (1% to 10%) associated with digoxin include anorexia, nausea, vomiting, visual disturbance (blurred or yellow vision), mental disturbance (such as anxiety, depression, delirium, and hallucination). Although toxic symptoms may appear within the therapeutic range, they are more frequent and serious with concentrations above 2.5 ng/mL, which occur with loading doses or dosing to steady state only [Lanoxin prescribing information, 2011]. In the current study, 2 single doses of 0.25 mg will be administered 21 days apart; therefore, these types of events are not expected.

2.2.4.8. Pravastatin

Pravastatin was chosen as a substrate for OATP1B1. Pravastatin is a reversible inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, pravastatin reduces very-low-density lipoprotein and triglycerides and increases high-density lipoprotein cholesterol. Peak plasma pravastatin concentrations occur 1 to 1.5 hours after oral administration and approximately 50% of the circulating drug is bound to plasma proteins. The major biotransformation pathways for pravastatin are (a) isomerization to 6epi pravastatin and the 3α-hydroxyisomer of pravastatin (lactone form which has 1/20 to 1/40 the HMG-CoA reductase inhibitory activity of pravastatin), and (b) enzymatic ring hydroxylation. Approximately 20% of the administered dose is excreted into the urine via metabolites. The t1/2 of pravastatin is approximately 2 hours. Standard adult dosage is 40 to 80 mg/day. Contraindications to pravastatin include hypersensitivity to any component of this medication. The most commonly reported adverse reactions include musculoskeletal pain, nausea/vomiting, upper respiratory infection, diarrhea, and headache. Although rhabdomyolysis can occur rarely after chronic high exposures to statins, large single doses of pravastatin (e.g., overdosage) are generally well-tolerated [Pravachol prescribing information, 2016]. In this study, participants will receive 2 single doses of 40 mg pravastatin administered 21 days apart, decreasing the probability of the aforementioned risks.

2.3. Benefit/Risk Assessment

Based upon preclinical and clinical studies (including studies with GSK3532795), the major risks for GSK3640254 are GI intolerability (e.g., abdominal pain and diarrhea) and toxicity (e.g., single-cell parietal cell necrosis), prolongation of the QTc, and neuropsychiatric safety. Reproduction of preclinical GI toxicity findings would be expected to be minimal and reversible. One preclinical study showed 1 dog with an increased QTc when given a single dose of GSK3640254. As described in Section 2.2.3.1, a cardiodynamic analysis showed a QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14 in Study 207187. Importantly, there were no abnormal clinically

significant arrhythmias or QTc prolongations (values >500 ms or increases >60 ms from Baseline). This study contains specific cardiac exclusion criteria, has ECG monitoring (at Tmax once GSK3640254 attains steady-state concentration), and has QTcF-based stopping criteria.

Finally, the protocol will exclude potential participants with any significant pre-existing psychiatric condition or positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee)-administered Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS assessment will also be administered by a clinician (or qualified designee) during the on-treatment portion of the study.

Since digoxin and metoprolol are both cardiotropic/cardioactive drugs, participants will be monitored by serial ECGs on probe substrate drug dosing days. To monitor for the respiratory effects of midazolam, continuous pulse oximetry and timed respiratory rate will be measured on probe substrate drug dosing days. More detailed information about the expected risks and benefits of the probe substrate drugs may be found in the prescribing information as cited in Section 2.2.4.

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, and neuropsychiatric safety), this study will include healthy adults who will receive clinical, ECG, and laboratory evaluations during their participation while confined to the clinic. More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK3640254 may be found in the CIB [GSK Document Number 2018N379610_01].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Preclinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with complementary 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. The no observed adverse effect level in the study was 12.5 mg/kg, which produced similar systemic exposures (8.79 µg/mL, 6.4 × the mean Cmax associated with the 200 mg multiple dose (1.4 µg/mL) in the FTIH study. Later, there were no GSK3640254-related effects on ECG parameters in dogs given up to 25 mg/kg/day for 4 weeks. In the FTIH study 207187 (doses up to 700 mg in SAD and 320 mg QD for 14 days in MAD), no participant exhibited QTc change from Baseline >60 ms or QTc >500 ms. As described in Section 2.2.3.1, in the concentration-QTc analysis, a 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).	***Screening:*** *Protocol exclusion criteria based on screening ECG parameters and cardiac medical history.* ***On-Treatment:*** *Participants will have ECG monitoring (at a clinically reasonable frequency) during the course of the study (see SoA, Section 1.3) with QTc stopping criteria (see Section 7.1.2).*
GI intolerability and toxicity	Observations 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 (Note: in the FTIH study 207187, AUC = 46.4 to 73.3 µg*h/mL; 2.6 to 4.2 × the mean AUC associated with the 200 mg multiple dose [17.5 µg*h/mL]). 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. No clinical trends in the system organ class of GI AEs have been seen across Phase 1 to 2a GSK3640254 clinical trials.	***Screening:*** *Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms.* ***On-Treatment:*** *Participants will undergo continuous evaluation for AEs during their participation in the study; there will be individual clinical stopping criteria based upon intensity of treatment-emergent AEs. A GI toxicity evaluation and monitoring plan will be available to guide investigators should GI AEs emerge (see Section 8.2.6).*
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 GSK3532795 across all studies, Grade 1 headache and Grade 1 sleep abnormalities	***Screening:*** *Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment) for participants. Participants will have a clinician (or qualified designee) administered C-SSRS and will be included given no positive (abnormal) response.*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. No clinical trends in the system organ class of neurologic or psychiatric AEs have been observed across the Phase 1 to 2a clinical trials.	***On-Treatment:*** *Participants will undergo physical examinations and laboratory testing. In addition, participants will undergo continuous evaluation for AEs during their participation in the study; there are individual clinical stopping criteria and monitoring based upon incidence and intensity of treatment-emergent psychiatric AEs (Section 7.1.4 and Section 8.2.5).* *Participants will be housed throughout study conduct to ensure rapid diagnosis and management of any potential event.* *The C-SSRS will be administered during and after the treatment phase of the study. In the event of new onset suicidal ideation, the participant will discontinue from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management. Guidance for the investigator on the management of emergent psychiatric symptoms will be available.*

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)

Digoxin and Metoprolol		
Cardiovascular (bradycardia, prolonged PR interval)	Digoxin: slows sinoatrial and atrioventricular conduction and commonly prolongs the PR interval. Metoprolol: may cause bradycardia and palpitations.	***Screening****: Protocol exclusion criteria based on screening ECG parameters and cardiac medical history.* ***On-Treatment****: Participants will be monitored by serial ECGs on probe substrate drug dosing days (see SoA, Section 1.3).*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Midazolam		
Respiratory depression and transient drowsiness	Midazolam may cause respiratory depression and transient drowsiness.	***Screening:*** *Eligible participants will be overtly healthy as determined by a medical professional based on medical evaluation.* ***On Treatment:*** *Participants will be housed throughout study conduct to ensure rapid diagnosis and management of any potential event. To monitor for the respiratory effects of midazolam, continuous pulse oximetry and timed respiratory rate will be measured on probe substrate drug dosing days (See SoA, Section 1.3).*

2.3.2. Benefit Assessment

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

2.3.3. Overall Benefit: Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the clinical data gathered from Phase 1 and 2a studies, and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 and coadministered single doses of the probe substrate drugs (in Regimens 1 and 3) are low, evaluable, and manageable.

The probe substrate drugs being administered in this study are used commonly in clinical practice and have a well-characterized and acceptable safety profile. As digoxin and metoprolol are both cardiotropic/cardioactive drugs, participants will be monitored via serial ECGs on probe substrate drug dosing days. To monitor for the respiratory effects of midazolam, continuous pulse oximetry and timed respiratory rate will be measured on probe substrate drug dosing days. Given that only healthy participants will be enrolled, that relatively low (relative to the usual therapeutic dose range), single doses are being administered, and that participants will be confined to a clinical facility after dosing with the probe substrate drugs, the safety risk of participation in this study is expected to be low. To minimize risk further, the protocol contains exclusions relevant to the study intervention and prohibits the concurrent intake of potentially interacting drugs or foods that might increase the concentrations of study intervention.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effect of GSK3640254 on the PK of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin under fed conditions in healthy participants	AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin
Secondary	
• To assess the safety and tolerability of GSK3640254 alone and in combination with caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin in healthy participants	• Safety and tolerability parameters for adverse events/serious adverse events, observed and change from baseline clinical laboratory assessments, electrocardiograms, and vital sign measurements
• To characterize the steady-state PK of GSK3640254 in the presence of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin in healthy participants	• AUC(0-t), AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 for GSK3640254
• To characterize the single-dose PK of the metabolites for the probe substrate drugs (α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, and 1-hydroxymidazolam)	• AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 for metabolites, and metabolite to parent ratios for Cmax and AUC(0-∞)

AUC(0-τ) = area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the plasma concentration-time curve from time zero to time t; Cτ = plasma concentration at the end of the dosing interval; Cmax = maximum observed concentration; PK = pharmacokinetics; Tmax = time of maximum observed concentration; t1/2 = apparent terminal phase half-life.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-sequence, one-way drug interaction study to investigate the effect of GSK3640254 200 mg on the PK of a metabolic probe cocktail containing the substrate drugs caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg.

The study will consist of a screening period and 3 sequential treatment regimens. Participants will be screened within 28 days before the first dose of study intervention.

Participants will receive the following treatments:

- Treatment A: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg on Day 1 (Regimen 1)
- Treatment B: GSK3640254 200 mg once daily on Days 11 to 20 (Regimen 2)
- Treatment C: Caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg co-administered with GSK3640254 200 mg on Day 21 (Regimen 3)

There will be a washout of 10 days between dosing of Regimen 1 and initiation of Regimen 2. There is no planned washout between Regimen 2 and Regimen 3. The participants will fast overnight for at least 8 hours prior to dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Pharmacokinetic blood samples for analysis of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin (and metabolites) will be obtained pre-dose and up to 120 hours after Regimen 1 and Regimen 3 dosing. Pharmacokinetic blood samples for analysis of GSK3640254 will be obtained pre-dose on Days 17 to 20 during Regimen 2, and pre-dose and up to 120 hours after Regimen 3 dosing.

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

Study assessments will be performed as indicated in the Schedule of Activities (Section 1.3). Participants will be confined to the clinic from check-in (Day –1) until discharge on Day 26.

4.2. Scientific Rationale for Study Design

This study is being conducted to investigate the potential DDIs when GSK3640254 is co-administered with a cocktail of CYP and transporter probe substrates in healthy participants. This study will aid in understanding these interactions and resulting changes in exposure (if any) when drugs that are metabolized via these pathways are given in combination with GSK3640254.

The inhibitory potential (direct and metabolism-dependent inhibition) of GSK3640254 towards 7 major human hepatic CYP enzymes was evaluated in human liver microsomes (CIB) [GSK Document Number 2018N379610_01]. GSK3640254 demonstrated minimal direct inhibition of all 7 CYP isoforms tested (half-maximal inhibitory concentration [IC50] values >13.3 µM). At the maximum projected clinical dose of 200 mg, there is a low risk for clinically meaningful CYP-mediated DDIs with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

GSK3640254 did not demonstrate human pregnane X receptor or vitamin D receptor mediated transactivation of CYP3A. Therefore, it is unlikely that GSK3640254 would induce CYP3A, or other pregnane X receptor and vitamin D receptor regulated enzymes/transporters in humans. In addition, GSK3640254 was tested in a panel of CYP induction assays using inducible cryopreserved human primary hepatocytes and showed no induction (50% inhibitory effect >5 µM) of CYP3A4, CYP2B6, and CYP1A2.

GSK3640254 is an inhibitor of OATP1B3 and multi-drug resistance protein (MRP)2 *in vitro* and has a potential of generating DDIs with substrates of these transporters at the projected human systemic exposures. The IC50 values of GSK3640254 against OATP1B3 and MRP2 were 0.55 and 2.2 µM, respectively. In addition, GSK3640254 was an inhibitor of UGT1A1 *in vitro* (IC50 = 3.9 µM) and clinical DDIs via this mechanism could be possible although literature reports have not revealed clinical DDIs with greater than 2-fold change in exposure, with a few exceptions, due to UGT1A1 inhibition [Lin, 2002; Williams, 2004]. A clinically meaningful DDI risk due to UGT1A1 inhibition by GSK3640254 is likely minimal. This is supported by the fact that following repeat oral administration of 50 mg dolutegravir (primarily metabolized by UGT1A1 with smaller contribution by CYP3A4), mean steady-state plasma exposure values for Cmax and AUC(0-τ) were similar when dolutegravir was administered alone or in combination with 200 mg GSK3640254.

This study is designed in accordance with the US Food and Drug Administration Guidance for Industry, Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications [DHHS, 2017] to assess the PK, safety, and tolerability of GSK3640254 and cocktail of CYP and transporter probe substrate drugs when administered alone and in combination. The probe substrate drugs used in this study are caffeine 200 mg (CYP1A2), metoprolol 100 mg (CYP2D6), montelukast 10 mg

(CYP2C8), flurbiprofen 100 mg (CYP2C9), omeprazole 40 mg (CYP2C19), midazolam 5 mg (CYP3A4), digoxin 0.25 mg (P-gp), and pravastatin 40 mg (OATP1B1).

4.3. Justification for Dose

A dose of 200 mg GSK3640254 was selected for this study as it is the maximum projected clinical dose. The t1/2 of GSK3640254 was approximately 22 hours in the MAD portion of Study 207187 (GSK Document Number 2020N430256_00) at the 200-mg dose, and predicted time to steady state is approximately 5 days. Dosing of GSK3640254 QD from Days 11 to 20 during Regimen 2 will be sufficient to bring plasma concentrations to steady state. There is no subsequent need for a washout of GSK3640254 since the primary remaining evaluation is for the co-administered probe substrate drugs and GSK3640254 at steady state.

Doses of the probe substrate drugs (caffeine 200 mg, metoprolol 100 mg, montelukast 10 mg, flurbiprofen 100 mg, omeprazole 40 mg, midazolam 5 mg, digoxin 0.25 mg, and pravastatin 40 mg) are standard for this type of study. Further information on the probe substrate drugs is provided in Section 2.2.4.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 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 the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination (including cardiopulmonary examination), laboratory tests, and cardiac monitoring (history and ECG).

Weight

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

Sex

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

4. Male or female

   a. Male participants

      1. Male participants should not engage in intercourse while confined in the clinic. There is no need for an extended period of double barrier use or prolonged abstinence after study discharge.

   b. Female participants:

      1. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

         - Is not a woman of childbearing potential (WOCBP) as defined in Appendix 3.

         OR

         - Is a WOCBP and using a nonhormonal contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 3, for 28 days before intervention, during the intervention period, and for at least 28 days after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

      2. A WOCBP must have a negative highly sensitive serum pregnancy test (Appendix 2) at Screening and check-in (Day –1).
      3. Additional requirements for pregnancy testing during and after study intervention are outlined in Appendix 2.

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

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 4 which includes compliance with the requirements and restrictions listed in the informed consent form (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).
2. A pre-existing condition interfering with normal GI anatomy or motility (e.g., gastro-esophageal reflux disease, gastric ulcers, gastritis) or hepatic and/or renal function that could interfere with the absorption, metabolism, and/or excretion of the study intervention or render the participant unable to take oral study intervention.
3. Prior cholecystectomy surgery (prior appendectomy is acceptable).
4. 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.
5. Any history of major depressive disorder with or without suicidal features, or anxiety disorders that required medical intervention (pharmacologic or not) such as hospitalization or other inpatient treatment and/or chronic (>6 months) outpatient treatment. Participants with other conditions such as adjustment disorder or dysthymia that have required shorter term medical therapy (<6 months) without inpatient treatment and are currently well-controlled clinically or resolved may be considered for entry after discussion and agreement with the ViiV Healthcare (VH)/GSK Medical Monitor.
6. Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the investigator (with or without psychiatric evaluation), could interfere with the participant's ability to comply with the dosing schedule and protocol evaluations or which might compromise the safety of the participant.
7. 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.
8. History of asthma, bronchospasm, or sleep apnea.
9. History of chronic musculoskeletal pain (myalgias).
10. History of rhabdomyolysis.
11. History of a bleeding disorder.
12. History of Raynaud's disease.

13. History indicative of an increased risk of a cardiac arrhythmia or cardiac disease, including the following:
    a. History of cardiac arrhythmias or palpitations associated with presyncope or syncope, or history of unexplained syncope.
    b. History of clinically relevant cardiac disease including symptomatic or asymptomatic arrhythmias (including but not limited to ventricular fibrillation, ventricular tachycardia, any degree of atrioventricular block, Brugada syndrome, Wolff-Parkinson-White syndrome, and sinus bradycardia, defined as heart rate less than 50 beats per minute [bpm] based on vital signs or ECG), presyncope or syncopal episodes, or additional risk factors for torsades de pointes (e.g., heart failure).
    c. History of clinically relevant structural cardiac disease including hypertrophic obstructive cardiomyopathy.
    d. History of hypokalemia.
    e. History of heart disease (e.g., coronary heart disease).

Laboratory Assessments

14. Presence of hepatitis B surface antigen at Screening or within 3 months prior to starting study intervention.
15. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention AND positive on reflex to hepatitis C RNA.
16. Positive HIV-1 and -2 antigen/antibody immunoassay at Screening.
17. Alanine aminotransferase (ALT) ≥1.5 × upper limit of normal (ULN). A single repeat of ALT is allowed within a single screening period to determine eligibility.
18. Bilirubin ≥1.5 × ULN (isolated bilirubin ≥1.5 × ULN 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.
19. Any acute laboratory abnormality at Screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
20. Any Grade 2 to 4 laboratory abnormality at Screening, with the exception of 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 is allowed within a single screening period to determine eligibility.
21. A positive test result for drugs of abuse (including marijuana), alcohol, or cotinine (indicating active current smoking) at Screening or before the first dose of study intervention.

Prior/Concomitant Therapy

22. Unable to refrain from the use of prescription or nonprescription drugs including vitamins, herbal and dietary supplements (including St John's wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study intervention and for the duration of the study. (Note: acetaminophen/paracetamol at doses of ≤2 g/day and topical hydrocortisone cream 1% are permitted for use any time during the study.)
23. Treatment with any vaccine within 30 days prior to receiving study intervention.
24. Unwillingness to abstain from excessive consumption of any food or drink containing grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study.

Prior/Concurrent Clinical Study Experience

25. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the study intervention (whichever is longer).
26. Prior exposure to GSK3640254 in another clinical study.
27. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.

Diagnostic Assessments

28. Any positive (abnormal) response confirmed by the investigator on a screening clinician- or qualified designee-administered C-SSRS.
29. Systolic blood pressure <100 mm Hg. Up to 2 repeats are allowed for confirmation.
30. 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, any degree of atrioventricular block, or conduction abnormality) which, in the opinion of the investigator or VH/GSK Medical Monitor, will interfere with the safety for the individual participant.
31. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males and Females
Heart rate[1]	<50 or >100 bpm
PR interval	>200 ms
QTc[2]	>450 ms

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

Other Exclusions

32. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.
33. Unable to refrain from tobacco or nicotine-containing products within 3 months prior to Screening.
34. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.
35. History of aspirin allergy.
36. 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 10.7.3.2.1)

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Abstain from consumption of red wine, grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study.
- Unless otherwise indicated, all doses of GSK3640254 and probe substrate drugs in this study will be administered in the fed state. The participants will fast overnight for at least 8 hours prior to dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours post-dose on serial PK sampling days (Day 1 and Day 21). The moderate fat meal will contain about 600 calories with approximately 30% of the calories coming from fat.
- No water is allowed from 1 hour prior to dosing until 1 hour after dosing with GSK3640254 and/or probe substrate drugs except for the glass of water needed to administer the study intervention (e.g., 240 mL). Water is allowed ad libitum at all other times. If necessary, additional water may be administered to allow dosing of all medications, but the additional volume of water must be kept to a minimum. The amount of additional water should be documented in the source documents.
- A standard lunch will be provided 4 hours after dosing. A standard dinner will be served approximately 10 hours after dosing. The food content of meals must be identical on serial PK sampling days.

5.3.2. Caffeine, Alcohol, and Tobacco

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

5.3.3. Activity

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

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

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

6.1. Study Interventions Administered

Intervention Name	GSK3640254	Probe Substrate Drugs							
		Caffeine	Metoprolol	Montelukast	Flurbiprofen	Omeprazole	Midazolam	Digoxin	Pravastatin
Type	Drug	Drug	Drug	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet	Tablet	Capsule	Syrup	Tablet	Tablet
Unit Dose Strengths	100 mg	200 mg	100 mg	10 mg	100 mg	40 mg	2 mg/mL	0.25 mg	40 mg
Dosage Levels	200 mg	200 mg	100 mg	10 mg	100 mg	40 mg	5 mg (2.5 mL)	0.25 mg	40 mg
Route of Administration	oral								
IMP and NIMP	IMP								
Sourcing	Sourced by Sponsor	Sourced by Investigator							
Packaging and Labeling	Provided in bulk by the Sponsor. The investigator will package in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.	In accordance with product label							

IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

6.2. Preparation/Handling/Storage/Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. All participants will receive the same treatments in the same sequence.

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

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

6.5. Concomitant Therapy

Acetaminophen/paracetamol at doses of ≤2 g/day and topical hydrocortisone cream 1% are permitted for use any time during the study and their use should be documented in the case report form (CRF). Other medications are not permitted without prior discussion with the VH/GSK Medical Monitor.

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

7.1.1. Liver Chemistry Stopping Criteria

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

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

Note, if ALT ≥3 × ULN AND bilirubin ≥2 × ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, the event will be reported as an SAE.

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

7.1.2. QTc Stopping Criteria

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

- The Baseline QTcF for each regimen will be based on averaged QTcF values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period obtained pre-dose on the first day of each respective regimen (i.e., Days 1, 11, and 21)

- An enrolled participant that develops an on-treatment QTcF >500 ms or an increase from Baseline QTcF >60 ms should have 2 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 Baseline for the respective regimen.

Refer to the SoA (Section 1.3) 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. Columbia-Suicide Severity Rating Scale

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 will be cause for immediate clinical assessment of suicidality (by the investigator or a consulting psychiatrist). Emergence of new onset suicidal ideation or a Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management.

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

7.1.4. Individual Participant Laboratory Abnormality and Adverse Event Stopping Criteria

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

- Any clinically significant AE or abnormalities in vital sign measurements, laboratory results or ECGs deemed to require discontinuation of study intervention; however, participants will continue to be clinically evaluated as necessary to ensure their safety
- Any Division of AIDS (DAIDS) Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement
- Any allergic or hypersensitivity reactions to study intervention
- Any DAIDS Grade 3 or higher psychiatric AE
- New onset suicidal ideation
- Any DAIDS Grade 3 or higher AE related to study intervention
- Any DAIDS Grade 4 AE
- DAIDS Grade 3 or higher laboratory abnormalities

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.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who is withdrawn from the study for any reason related to safety (listed in Section 7.1.4 or otherwise) will be continued to be followed to assess the outcome of the safety event that triggered discontinuation of study intervention.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed. In addition, pulse oximetry will be assessed on Day 1 and Day 21 as per the SoA (Section 1.3).
- Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- At each time point at which triplicate measurements are required, 3 consecutive blood pressure and pulse readings will be recorded at intervals of at least 1 minute. Each measurement will be recorded in the CRF.
- When vital signs are scheduled at the same time as blood collections for laboratory tests, vital signs are to be taken first. Pharmacokinetic blood collection should occur as close to the nominal time as possible.

8.2.3. Electrocardiograms

- Twelve-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- Twelve-lead ECGs will be performed with the participant in a supine position after a rest of at least 10 minutes.
- At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minutes) recording period. Each measurement will be recorded in the CRF.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal by the investigator during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or

baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

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 a previous MI compound, 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 DAIDS 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 the AE through interview, additional unscheduled clinical laboratory tests, and/or imaging. Psychiatric consultation may be required at the discretion of the investigator. Any pharmacotherapy should be discussed with the medical monitor.
- Any DAIDS Grade 3 or 4 psychiatric AE: As described in Section 7.1.4, a Grade 3 or 4 psychiatric AE will result in discontinuation from the study and emergency psychiatric evaluation (including potential hospitalization and pharmacotherapy as indicated).

8.2.6. Gastrointestinal Toxicity Evaluation and Monitoring Plan

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

management (including discontinuation of a participant) of any GI symptoms throughout the study.

For any DAIDS Grade 4 or related Grade 3 AE, the investigator will discontinue the participant from the study and perform an evaluation/management plan incorporating the elements in Table 1.

Table 1 Gastrointestinal Toxicity Evaluation and Management

HISTORY	**For symptoms of all grades, a thorough history forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical study.**
Nausea and Vomiting	The investigator should attempt to identify the etiology of these symptoms (and whether it is intraperitoneal, extraperitoneal, medication related, infection related, or due to a metabolic disorder [Hasler, 2012]. Medications can cause nausea and vomiting acutely.
Dyspepsia	The investigator should identify the presence of red flags (odynophagia, unexplained weight loss, recurrent vomiting, GI bleeding, jaundice, palpable mass or adenopathy, or family history of GI malignancy). Symptoms of dyspepsia could include early satiety, bloating, or belching. Additionally, atypical symptoms of dyspepsia could include: pharyngitis, asthma, bronchitis, hoarseness, chest pain, or abdominal pain.
Other Clinical Syndromes	Additional diagnostic criteria for other GI disorders potentially encountered in the clinical study are available elsewhere [Rome Foundation, 2019].
PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history [Hasler, 2012]. Acutely, the investigator may assess for signs of intravascular volume depletion (e.g., orthostasis) and/or aspiration of vomitus as appropriate. Abdominal tenderness and guarding may indicate inflammation. The presence of fecal blood can indicate mucosal damage (e.g., from an ulcer). Complete evaluation of dyspepsia should include an oral examination (poor dentition or pharyngeal erythema) and lungs for wheezing.**
DIAGNOSTIC EVALUATION AND MANAGEMENT	**A major goal in the diagnostic evaluation of a participant with upper GI symptoms is to quickly arrive at a final diagnosis without exposing the participant to unnecessary (invasive) testing; investigators should exercise good clinical judgment in this regard [Soll, 2009]. A major goal of therapy is directed at correcting the underlying identifiable medical or surgical abnormalities. Consultation (e.g., gastroenterologist) is recommended as clinically indicated.**
Grade 1 symptoms	Participants may be treated symptomatically. If participants develop dyspepsia alone, generally only limited and direct diagnostic testing should be performed. If the participant has dyspepsia they should limit alcohol, caffeine, chocolate, tobacco, and eating directly before bedtime.
Grade 2 symptoms	Diagnostic testing may include but is not limited to the following (as clinically indicated): • Serum chemistries and assessment of hemoglobin if not recently performed • Testing for *Helicobacter pylori* • Polymerase chain reaction for viruses (e.g., cytomegalovirus) For participants who are infected with *H. pylori*, discontinuation from the study is necessary. Management should be targeted at addressing the underlying pathology.
Grade 3 symptoms	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • Computed tomography scan to identify GI inflammation • Upper endoscopy with biopsy as indicated (e.g., mucosal injury or the presence of red flags) Management should be targeted at addressing the underlying pathology.
Grade 4 symptoms	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.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 6. As described in Appendix 6, intensity of AEs (and laboratory abnormalities) will be graded using the most recent version of the DAIDS grading table (Appendix 7) at the time of the last participant last visit. While the study population will consist of HIV-1 seronegative healthy participants, the DAIDS criteria is being used in later phase clinical studies (e.g., Phase 2); additionally, the DAIDS criteria have a more conservative grading scale relative to other scales (e.g., Common Terminology Criteria for Adverse Events [CTCAE] v 4.0). Thus, participant safety evaluation and monitoring will be more conservative.

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

See Section 10.7.3.2 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 ICF until the end of the study at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the end of the study at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be considered medical history, not an AE, and will be recorded in the source documents.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.
- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 8.3.6), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 6.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs), 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 an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the CIB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

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

- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest include all AEs classified in the cardiovascular (per the the Medical Dictionary for Regulatory Activities) system organ class, seizure, and syncope. Additional AEs of special interest within other system organ classes (e.g., GI, neurologic, or psychiatric) may be defined in the reporting and analysis plan.

8.4. Treatment of Overdose

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

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

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3640254 or any of the probe substrate drugs can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis immediately and through 7 days after the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

8.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the SoA (Section 1.3).
- Separate whole blood samples of approximately 13 mL will be collected for measurement of plasma concentrations of the probe substrate drugs (caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin and metabolites α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, and 1-hydroxymidazolam) as specified in the SoA (Section 1.3). In addition, Coproporphyrin-1 (CP-1) will be investigated as an exploratory aim as a biomarker of OATP inhibition, alongside pravastatin.

- A maximum of 10 samples (approximately 20 mL) may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3640254 and the probe substrate drugs. Samples collected for analyses of plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK3640254 and the probe substrate drugs, any remaining plasma may be analyzed for other compound-related metabolites and the results provided in a separate report.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal hypothesis that will be statistically tested in this study.

Administration of GSK3640254 under fed conditions may change the exposure to caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin and pravastatin.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

As there is no formal research hypothesis being statistical tested in this study, the sample size is not selected based on statistical considerations but was determined using feasibility. Approximately 20 participants will be enrolled to ensure that 18 evaluable participants complete the study. If participants prematurely discontinue the study,

additional participants may be enrolled after consultation with the sponsor to ensure that the required number of evaluable participants complete the study.

9.2.2. Sample Size Sensitivity

The statistical analysis will be performed to compare Treatment C versus Treatment A. For a sensitivity analysis, with a sample size of 18 evaluable participants and across a range for intrasubject coefficient of variability (CVw) of 10%, 20%, 30%, and 40% and a range for as point estimates (PEs) of 0.9, 1.0, and 1.1 were explored. It is estimated that the precision (i.e., half-width of the 90% confidence interval (CI) on the log and ratio scale), and CI on the original scale for each PE will be:

CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
10	0.058	0.059	0.9	(0.849, 0.954)
			1.0	(0.944, 1.06)
			1.1	(1.038, 1.166)
20	0.115	0.122	0.9	(0.802, 1.01)
			1.0	(0.891, 1.122)
			1.1	(0.981, 1.234)
30	0.170	0.185	0.9	(0.759, 1.067)
			1.0	(0.844, 1.185)
			1.1	(0.928, 1.304)
40	0.223	0.250	0.9	(0.72, 1.125)
			1.0	(0.8, 1.25)
			1.1	(0.88, 1.375)

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

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

9.4. Statistical Analyses

9.4.1. Pharmacokinetic Analyses

Plasma GSK3640254 and probe substrate drugs (caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin; and metabolites α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, and 1-hydroxymidazolam) concentration-time data will be analyzed by PPD, under the oversight of Clinical Pharmacology Modeling & Simulation department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher. Statistical analysis will be performed by PPD, under the oversight of Clinical Statistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

Endpoint	Statistical Analysis Methods

Primary	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of probe substrates will be subjected to PK analyses using noncompartmental methods.
	• Based on the individual concentration-time data the following primary plasma PK parameters will be estimated:
	  • AUC(0-t), AUC(0-∞), and Cmax
	• Analysis will be performed to compare the PK exposure of probe drugs with and without GSK3640254. Analyses will be performed on the natural logarithms of AUC(0-t), AUC(0-∞), and Cmax using linear mixed-effect models with treatment as a fixed effect and measurements within participant as repeated measures. Effects will be estimated, and 90% CIs will be constructed for the following treatment comparison:
	  • Treatment C versus Treatment A
	Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.

Endpoint	Statistical Analysis Methods
	• Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma probe substrate primary plasma PK parameter (AUC[0-t], AUC[0-∞], Cmax, Tmax, and t1/2) values will be summarized by treatment.

Secondary	• Plasma concentrations of the metabolites for the probe substrates (α-hydroxymetoprolol, 36-hydroxymontelukast, 5-hydroxyomeprazole, and 1-hydroxymidazolam) will be subjected to PK analyses as described above for the parent analytes. Based on the individual concentration-time data the following plasma PK parameters will be estimated:
	  • Treatment A and C: AUC(0-t), AUC(0-∞), Cmax, Tmax, and t1/2 and metabolite-to-parent ratios for Cmax and AUC(0-∞)
	• Plasma concentrations of GSK3640254 will be subjected to PK analyses using noncompartmental methods. Based on the individual concentration-actual time data the following plasma PK parameters will be estimated:
	  • Treatment C: AUC(0-t), AUC(0-τ), Cmax, Cτ, Tmax, and t1/2
	  • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 PK parameter values will be presented.
	• Additionally, pre-dose (trough) PK plasma concentrations of GSK3640254 (Treatment B) will be summarized and used to assess achievement of steady state.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

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

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

9.4.3. 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 [FDA, 2020; EMA March 2020; EMA April 2020].

9.5. Interim Analyses

No interim analysis is planned.

9.6. Data Monitoring Committee

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse event
ALT	Alanine aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC(0-τ)	Area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time t
bpm	Beats per minute
CI	Confidence interval
CIB	Clinical Investigator's Brochure
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CP-1	Coproporphyrin-1
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
Cτ	Plasma concentration at the end of the dosing interval
CVw	Intrasubject coefficient of variation
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HRT	Hormonal replacement therapy
IC50	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation

IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
MAD	Multiple-ascending dose
MI	Maturation inhibitor
MRP	Multi-drug resistance protein
NCA	National Competent Authority
NSAID	Nonsteroidal anti-inflammatory drug
OATP	Organic anion-transporting polypeptide
P-gp	P-glycoprotein
PE	Point estimate
PI	Principal Investigator
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using the Fridericia formula
QTL	Quality tolerance limits
SAD	Single-ascending dose
SAE	Serious adverse event
SoA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
Tmax	Time of maximum observed concentration
TQT	Thorough QT
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
VH	ViiV Healthcare
WOCBP	Woman of childbearing potential

- **Trademark Information**

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
DAIDS
Phoenix WinNonlin
Portia
Pravachol
Singulair
Vivarin

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 2 Protocol-Required Safety Laboratory Assessments

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

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

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 5. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local serum testing will be standard for the protocol.

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

10.3.1. Definitions:

Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Nonhormonal intrauterine device
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. The documentation on male sterility can come from the site personnel's: review of participant's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* • For the 28 days after study exit, women may resume oral hormonal contraceptives but double barrier methods (a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide) must be used in addition.
Highly Effective Methods[b] That Are User Dependent: *Failure rate of <1% per year when used consistently and correctly.*
• Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* *Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

10.3.3. Collection of Pregnancy Information:

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to VH/GSK within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to VH/GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to VH/GSK as described in Appendix 6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

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

10.4.1. Regulatory and Ethical Considerations

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

10.4.2. Financial Disclosure

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

10.4.3. Informed Consent Process

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

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

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

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

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

10.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his or 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 or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4.5. Committees Structure

Not applicable.

10.4.6. Dissemination of Clinical Study Data

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

10.4.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must 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/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.4.8. Source Documents

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

10.4.9. Study and Site Start and Closure

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

The first act of recruitment is the first participant screened and will be the study start date.

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/IEC, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

10.4.10. Publication Policy

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

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3 × ULN
If ALT ≥3 × ULN AND bilirubin[1,2] ≥2 × ULN (>35% direct bilirubin) or international normalized ratio (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 intervention
• Report the event to VH/GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within Baseline (see MONITORING below)
MONITORING:
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within Baseline
• A specialist or hepatology consultation is recommended
If ALT ≥3 × ULN AND bilirubin <2 × ULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend
• Obtain blood sample for PK analysis, obtained within 48 hours of last dose[4]
• Serum creatine phosphokinase and lactate dehydrogenase
• Fractionate bilirubin, if total bilirubin ≥2 × ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over-the-counter medications
• Record alcohol use on the liver event alcohol intake CRF
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney</td></tr>
</table>

Liver Chemistry Stopping Criteria	
phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within Baseline	microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRF.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3 × ULN and bilirubin ≥ 2 × ULN. 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 ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody, hepatitis B surface antigen, and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and hepatitis E IgM antibody.
4. Pharmacokinetic sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

10.6.1. Definition of AE

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

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

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

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.6.2. Definition of SAE

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

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

Results in death

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

Requires inpatient hospitalization or prolongation of existing hospitalization

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

Results in persistent or significant disability/incapacity

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

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.

10.6.3. Recording and Follow-up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the DAIDS grading table Version 2.1, July 2017 (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) and assign it to 1 of the following categories:

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

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

Assessment of Causality

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by VH/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide VH/GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to VH/GSK within 24 hours of receipt of the information.

10.6.4. Reporting of SAE to VH/GSK

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

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

10.7. Appendix 7: 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 (NCAs), as necessary.

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

10.7.1. 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 NCA/IRB/IEC regulations.

10.7.2. 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.

10.7.3. COVID-19 Specific Data Capture

10.7.3.1. Capturing COVID-19 Specific Protocol Deviations

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

10.7.3.2. 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 AEs/SAEs 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
3. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation in the setting of clinically defined mild COVID-19 infection.
4. 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.

10.7.3.2.1. 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.

10.8. Appendix 8: Division Of AIDS (DAIDS) Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 2.1 July 2017

The DAIDS grading table can be found at the following link:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

10.9. Appendix 9: Protocol Amendment History

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

Amendment 1 02-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 to this amendment.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Addition of daily temperature check.	Daily temperature check as added as a measure to monitor COVID-19 infection.
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	Age change	Max entry age of study participants was changed from 55 to 50 years of age.
5.2 Exclusion Criteria	Liver chemistry updated WHO COVID-19 update	Liver chemistry updated as per the VSLC liver safety guidance April 2020. Addition of WHO COVID-19 exclusion guidance.
7.1.5 Discontinuation of Study Intervention	Addition of COVID-19 as discontinuation criteria.	Addition of permanently discontinuing from study due to COVID-19 infection.
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 adverse events and serious adverse events related to COVID-19.
8.5 Pharmacokinetics	Addition of CP-1 Assay & total blood volume collected.	Addition of Coproporphyrin-1 as a biomarker of OATP inhibition for exploratory aim.
9.4.3 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

Section # and Name	Description of Change	Brief Rationale
		affect the study and data integrity.
10.4.7 Data Quality Assurance	Quality tolerance limits (QTLs)	Addition of QTLs to be pre-defined and summarized in the clinical study report.
10.7 COVID-19 Pandemic and Clinical Trial Continuity	Addition of appendix to document requirements to mitigate for any actions related to COVID-19	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.

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