TITLE PAGE

Protocol Title: A Study to Evaluate the Effect of Therapeutic and Supratherapeutic Oral Doses of GSK3640254 on Cardiac Conduction as Assessed by 12-Lead Electrocardiogram Compared to Placebo and a Single Oral Dose of Moxifloxacin in Healthy Adult Participants

Protocol Number: 213053

Compound Number or Name: GSK3640254

Study Phase: Phase 1

Short Title: Effect of Therapeutic and Supratherapeutic Oral Doses of GSK3640254 on Cardiac Conduction

Sponsor Name and Legal Registered Address:

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

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

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

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

Regulatory Agency Identifying Number: IND 139,838

Approval Date: 10-SEP-2020

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Study to Evaluate the Effect of Therapeutic and Supratherapeutic Oral Doses of GSK3640254 on Cardiac Conduction as Assessed by 12-Lead Electrocardiogram Compared to Placebo and a Single Oral Dose of Moxifloxacin in Healthy Adult Participants

Short Title: Effect of Therapeutic and Supratherapeutic Oral Doses of GSK3640254 on Cardiac Conduction

Rationale: The International Council for Harmonisation (ICH) E14 guidance, as adopted in the US Food and Drug Administration (FDA) Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, emphasizes the need to obtain clear and robust data through "thorough" studies that assess the effect of new chemical entities on electrocardiogram (ECG) parameters. Specifically, "thorough" studies are defined as trials dedicated to evaluating a compound's effect on cardiac repolarization, as measured by the corrected QT interval (QTc). Although many Phase 1, 2, and 3 studies may be conducted with a new compound, they typically utilize insufficient sample sizes, infrequent sampling of ECG data, or inadequate controls to overcome high variance in cardiac repolarization due to spontaneous change. Therefore, this thorough QT (TQT)/QTc study will be conducted to evaluate the effect of GSK3640254 on cardiac repolarization.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
Part 1: • To determine the safety and pharmacokinetics of a supratherapeutic dose of GSK3640254 administered for 7 days in healthy participants	Part 1: • Area under the plasma concentration-time curve from time zero to time t (AUC[0-t]), area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state (AUC[0-τ]), maximum observed concentration (Cmax), plasma concentration at the end of the dosing interval (Cτ), and time of maximum observed concentration (Tmax) of GSK3640254 in plasma • Remaining Plasma will be analyzed for compound related metabolites • Safety and tolerability parameters for adverse events (AEs)/serious adverse events (SAEs), observed and change from baseline in clinical laboratory assessments, electrocardiograms (ECGs), and vital sign measurements
Part 2: • To determine the effect of therapeutic and supratherapeutic concentrations of	Part 2: • Placebo-corrected change from baseline in QTcF (ΔΔQTcF) for GSK3640254 using

Objectives	Endpoints
multiple dose GSK3640254 on the QT interval corrected with Fridericia's formula (QTcF) in healthy participants	concentration-QTc (C-QTc) analysis (primary analysis) • Remaining Plasma will be analyzed for compound related metabolites
Secondary	Secondary
Part 2: • To evaluate the effect of multiple oral therapeutic and supratherapeutic doses of GSK3640254 on other ECG parameters (heart rate [HR], PR, QRS, and QTcF intervals, treatment-emergent T-wave morphology, and appearance of U-waves)	Part 2: • Change from baseline in HR, QTcF, PR, QRS (ΔHR, ΔQTcF, ΔPR, and ΔQRS) intervals using by-time point analysis (secondary analysis); the placebo-corrected change from baseline in HR, PR, QTcF, and QRS (ΔΔHR, ΔΔPR, ΔΔQTcF, and ΔΔQRS) using by-timepoint analysis; categorical outliers for QTcF, HR, PR, and QRS; and the frequency of treatment-emergent changes of T-wave morphology and U-wave presence
• To demonstrate assay sensitivity of the study design to detect a QTc effect using a single 400 mg oral moxifloxacin as a positive control.	• ΔΔQTcF for moxifloxacin (primary: C-QTc analysis and secondary: by-time point analysis)
• To evaluate the pharmacokinetics of multiple oral therapeutic and supratherapeutic doses of GSK3640254 and a single dose of moxifloxacin.	• AUC(0-t), AUC(0-τ), Cmax, Cτ, and Tmax of GSK3640254 in plasma • Cmax and Tmax of moxifloxacin in plasma
• To assess the safety and tolerability of multiple therapeutic and supratherapeutic doses of GSK3640254	• Safety and tolerability parameters for AEs/SAEs, observed and change from baseline in clinical laboratory assessments, ECGs, and vital sign measurements

Overall Design: This study has an adaptive 2-part design, where projected doses will be identified and may be modified according to assessment of accrued data. Part 1 will consist of up to 2 sentinel cohorts to determine the supratherapeutic dose for Part 2, which will be the main QTc study.

Part 1, Sentinel Cohorts: Part 1 will be a randomized, double-blind study in up to 2 sequential cohorts of approximately 8 healthy participants each (3:1 ratio to receive GSK3640254 or placebo) to evaluate the safety, tolerability, and pharmacokinetics (PK) following multiple-dose administration of GSK3640254 for 7 days.

Part 1 of the study will consist of a screening period and a treatment period for each cohort conducted. The first cohort will evaluate once daily (QD) dosing of GSK3640254 or placebo. On Day 1 of the treatment period, 8 participants will be randomly assigned in a 3:1 ratio to receive GSK3640254 500 mg or placebo. All doses of study intervention will be administered under fed conditions. The participants will fast overnight for at least 8 hours prior to breakfast before the morning dose and will receive a moderate-fat meal (defined as approximately 600 calories, 30% from fat) 30 minutes prior to dosing. Participants will eat this meal within 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

The second cohort if conducted would evaluate twice daily (BID) dosing of GSK3640254. The second cohort would only be used if GSK3640254 PK or safety/tolerability endpoints defined above showed that an alternative supratherapeutic dose (other than 500 mg QD) would need to be evaluated in Part 2. The maximum dose would be 500 mg BID. The morning dose will be administered with a moderate-fat meal as previously described for Cohort 1. Participants will fast at least 2 hours prior to dinner before the evening dose. Participants will eat this meal within 25 minutes or less and dose administration will occur within 5 minutes of completion of meal consumption.

Pharmacokinetic blood samples for the analysis of GSK3640254 will be collected at selected time points pre-dose and up to 48 hours after the Day 7 morning dose.

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

Study participants will be confined to the clinic from Day -1 until discharge on Day 9. The total duration of the study for a participant in Part 1, including screening, is 37 days.

Part 2, Main QTc Study: Part 2 will be a double-blind (to GSK3640254 and Placebo only), randomized, placebo-controlled study to investigate the safety, tolerability, and PK of GSK3640254 doses on cardiac conduction as compared to placebo and a single oral dose of moxifloxacin in healthy adult participants. Moxifloxacin is included as a positive control and will be open label. Approximately 42 participants will be randomized to ensure 34 evaluable participants with data from all treatment periods. Participants will be randomly assigned to 1 of 12 treatment sequences, with at least a 7-day washout after the final dose in each period. The supratherapeutic dose will be determined based on the results of preliminary safety and PK data from Part 1 and will be decided upon by the study team and the investigator.

All doses of study intervention will be administered under fed conditions. The participants will fast overnight for at least 8 hours prior to breakfast before the morning dose and will receive a moderate-fat meal (defined as approximately 600 calories, 30% from fat) 30 minutes prior to dosing. If participants will receive a BID dose, they will fast at least 2 hours prior to dinner before the evening dose. In both cases, participants will eat this meal within 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Part 2 of the study will consist of a screening period, a check-in visit (Day -2), a baseline visit (Day -1), and 4 sequential treatment periods. Prior to dosing on Day 1 of Period 1, participants will be randomly assigned to a treatment sequence.

Continuous Holter ECG monitoring will be performed on Day -1 (full set of replicates mirroring pre- and post-dose time points). In each treatment period, continuous Holter ECG monitoring will be performed pre-dose on Day 1, and pre-dose and up to 24 hours after dosing on Day 7.

Pharmacokinetic blood samples for the analysis of GSK3640254 and moxifloxacin will be collected at selected time points pre-dose and up to 24 hours after the Day 7 morning dose.

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory results, vital sign measurements, safety 12-lead ECG results, and physical examination findings. The same ECG machine will be used for any individual participant in order to minimize undue machine generated bias.

Study participants will be confined to the clinic starting on Day -2 of Period 1. Final discharge will be on Day 9 of Period 4. The total duration of the study for a participant in Part 2, including screening, is approximately 82 days.

Disclosure Statement: This is a 2-part study. Part 1 is a sequential treatment study with 2 arms that is participant and investigator blinded. Part 2 is a single group, single arm, crossover treatment study that is participant and investigator blinded (open-label for moxifloxacin).

Number of Participants: In Part 1, up to 16 participants may be enrolled (8 participants per cohort). In Part 2, approximately 42 participants will be enrolled to achieve 34 evaluable participants.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study are not considered enrolled unless otherwise specified by the protocol.

Intervention Groups and Duration:

Part 1:

- Sentinel Cohort 1: GSK3640254 500 mg or placebo orally QD for 7 days.
- Sentinel Cohort 2 (optional): If needed, a dose of GSK3540254 or placebo orally BID for 7 days (13 doses), with only a single morning dose administered on the seventh day. The specific dose in sentinel Cohort 2 will be determined based on the results of preliminary safety and PK data from sentinel Cohort 1 and decided upon by the study team and the investigator. The dose will no exceed 500 mg BID.

Part 2: Participants will receive treatments in 1 of the 12 following sequences:

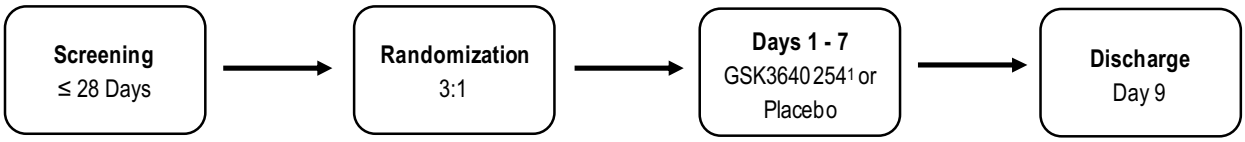
Sequence	Period 1	Period 2	Period 3	Period 4
1	T	ST	P	M
2	ST	M	T	P
3	P	T	M	ST
4	M	P	ST	T
5	ST	P	T	M
6	P	M	ST	T
7	T	ST	M	P
8	M	T	P	ST
9	P	T	ST	M
10	T	M	P	ST
11	ST	P	M	T
12	M	ST	T	P

Treatment T: Therapeutic dose of GSK3640254 (100 mg once daily) Days 1 through 7.
Treatment ST: Supratherapeutic dose of GSK3640254 (to be determined from Part 1) Days 1 through 7.
Treatment P: Placebo for GSK3640254 Days 1 through 7.
Treatment M: Moxifloxacin; GSK3640254 placebo Days 1 through 6 and a single dose of Moxifloxacin (400 mg) on Day 7.
To maintain the blind, the number of tablets administered for therapeutic, supratherapeutic, (Days 1 through 6 only), and placebo doses will be identical. The total number of tablets will be based on the actual supratherapeutic dose derived from Part 1 of the study. For example, if the supratherapeutic dose is determined to be 500 mg QD, the therapeutic dose would consist of one 100 mg GSK3640254 tablet and four placebo tablets, the supratherapeutic dose would consist of five 100 mg GSK3640254 tablets, and the placebo dose would consist of five placebo tablets.

Data Monitoring or Other Committee: No

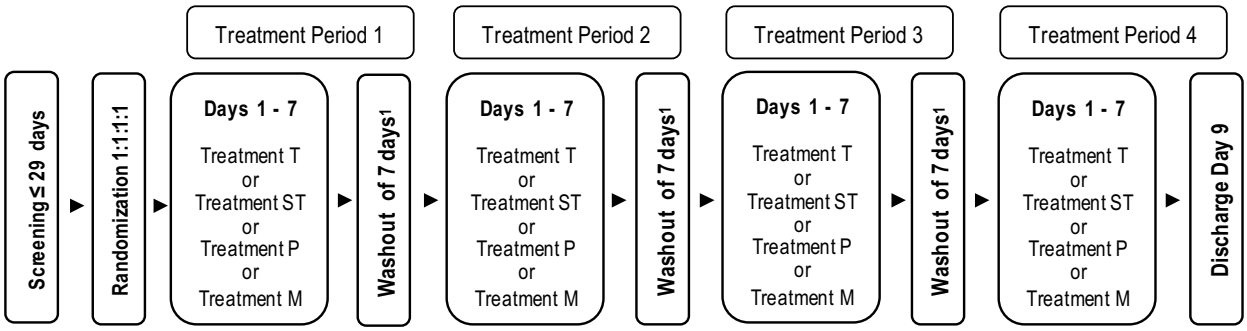
1.2. Schema

Figure 1 Study Design Schematic – Part 1



1. Sentinel Cohort 1: GSK3640254 500 mg or placebo once daily.
   Sentinel Cohort 2 (if needed): GSK3640254 or placebo twice daily, with only a single morning dose administered on the seventh day; dose to be determined after completion of Sentinel Cohort 1.

Figure 2 Study Design Schematic – Part 2



1. Washout will be at least 7 days minus 4 hours to allow for flexibility in scheduling in the clinic.
Treatment T: Therapeutic dose of GSK3640254 (100 mg once daily) Days 1 through 7.
Treatment ST: Supratherapeutic dose of GSK3640254 (to be determined from Part 1) Days 1 through 7
Treatment P: Placebo for GSK3640254 Days 1 through 7.
Treatment M: Moxifloxacin; GSK3640254 placebo Days 1 through 6 and a single dose of Moxifloxacin (400 mg) on Day 7.

1.3. Schedule of Activities (SoA)

- Screening procedures may be done over more than 1 visit, but must all be completed within 28 days prior to Day 1 in Part 1, and 29 days prior to Day -2 in Part 2. Subjects outside of these screening windows will not be able to participate in their respective portions of the study.
- 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 – Part 1

Procedure	Screening (up to 28 days before Day 1)
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight[1]	X
Laboratory assessments (haematology, chemistry, urinalysis)	X
12-lead electrocardiogram	X
24-hour Holter monitor recording[2]	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
Human immunodeficiency virus, hepatitis B and C screening	X
Molecular test for SARS-CoV-2[3]	X

1. A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.
2. May be performed either during Screening or on Day -1 upon admission.
3. Two consecutive approved molecular tests (polymerase chain reaction or antigen test). The first test should be performed ≥7 days prior to admission.

Time and Events Table – Part 1, Supratherapeutic Dose Selection

Procedure	Check-in	Baseline	Treatment							Follow-up		Notes
	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	
Admit to clinic	X											
Discharge from clinic											X	Discharge from clinic following completion of the last study procedure on Day 14.
Brief physical examination	X								X		X	An interim symptom-targeted brief physical examination will be performed at the discretion of the investigator. See Section 8.2.1 for a description of the brief physical examination.
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	Blood pressure and pulse will be measured in triplicate pre-dose on Day 1. Single blood pressure and pulse will be measured on other study days.
Daily temperature check	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X	X			X			X		X	The pre-dose ECG on Day 1 will be collected in triplicate. Other ECGs will be single. The ECGs on Days 1, 4, and 7 will be collected at pre-dose and post-dose at 2, 4, and 6 hours.
Drug, alcohol, and cotinine screen	X											See Appendix 2 for specific tests to be performed.

Procedure	Check-in	Baseline	Treatment							Follow-up		Notes
	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	
Molecular Test for SARS-CoV-2	X[1]							X			X	[1]This second test should be performed 24 hours prior to admission to the unit. Participants should be quarantined within the unit until the second test result is negative. Once the second test result is confirmed to be negative, they can be released into the unit and follow infection control practices.
Laboratory assessments (haematology, chemistry, urinalysis)	X				X				X		X	See Appendix 2 for specific tests to be performed.
Pregnancy test	X										X	Serum testing on Day -1.
Columbia-Suicide Severity Rating Scale	X			X		X		X		X		
Randomization			X									
Study intervention: Sentinel Cohort 1: GSK3640254 500 mg or placebo once daily Sentinel Cohort 2 (optional): To be determined after completion of Cohort 1 and not to exceed 500 mg BID.			X	X	X	X	X	X	X			

Procedure	Check-in	Baseline	Treatment							Follow-up		Notes
	Day -2	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9[1]**	
GSK3640254 PK sampling			X				X	X	X	X	X	Blood collection for PK analysis of GSK3640254 will be collected within 40 minutes prior to the morning dose on Days 1, 5, 6, and 7, and after dosing on Day 7 at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 12, 24, and 48 hours.
AE review			←==========X==========→									
SAE review	←==========X==========→											
Concomitant medication review	←==========X==========→											

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

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

Screening Visit – Part 2, Thorough QT Study

Procedure	Screening (up to 29 days before Day -2)
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
24-hour Holter monitor recording[2]	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
Human immunodeficiency virus, hepatitis B and C screening	X
Molecular test for SARS-CoV-2[3]	X

1. A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.
2. May be performed either during Screening or on Day -2 upon admission.
3. Two consecutive approved molecular tests (polymerase chain reaction or antigen test). The first test should be performed ≥7 days prior to admission.

Time and Events Table – Part 2, Thorough QT study

Procedure	Check -in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
Admit to clinic	X																			
Discharge from clinic																			X	Final discharge from clinic following completion of the last study procedure on Day 9 of Period 4.
Brief physical examination	X									D14									X	An interim symptom-targeted brief physical examination will be performed at the discretion of the investigator. See Section 8.2.1 for description of the brief physical examination.
Vital signs	X	X	X	X	X	X	X	X	X	D8, D14 only	X	X	X	X	X	X	X	X	X	Blood pressure and pulse will be measured in triplicate pre-dose on Day 1 of each period and single blood pressure and pulse will be measured on other study days. On Day 7 of each period, blood pressure and pulse to be measured before dosing and 4 and 24 hours after dosing.
Daily temperature check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	While confined to clinic.

Procedure	Check-in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
Safety 12-lead ECG	X	X	X	X		X	X		X	D8, D14	X	X		X	X		X	X	X	The pre-dose ECGs on Day 1 of each period will be collected in triplicate. All other ECGs will be single. On Days 1, 4, and 7, ECGs will be collected at pre-dose and post-dose at 1, 2, 3, 4, 6, and 24 hours.
Drug, alcohol, and cotinine screen	X									D14										See Appendix 2 for specific tests to be performed. Day 14 drug, alcohol, and cotinine screen required only for participants that are furloughed during the washout period.
Laboratory assessments (hematology, chemistry, urinalysis)	X									D8, D14									X	See Appendix 2 for specific tests to be performed.

Procedure	Check-in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
Molecular Test for SARS-CoV-2	X[1]							X		D13						X			X	[1]The second test should be performed 24 hours prior to admission to the unit. Participants should be quarantined within the unit until the second test result is negative. Once the second test result is confirmed to be negative, they can be released into the unit and follow infection control practices. Test to be obtained every 7 days from Check-in (regardless of period or washout) while in-house.
Pregnancy test	X									D14									X	Serum testing on Day -2. Day 14 pregnancy test required only for participants that are furloughed during the washout period.
Columbia Suicide Severity Rating Scale	X									D8									X	
Randomization			X																	Period 1 only.
Study intervention: GSK3640254 therapeutic or supratherapeutic dose, placebo, or moxifloxacin			X	X	X	X	X	X	X		X	X	X	X	X	X	X			Moxifloxacin treatment consists of GSK3640254 placebo on Days 1 through 6 with moxifloxacin on Day 7 only.
Holter ECG recording[3]		X	X						X	D8	X						X	X		

Procedure	Check-in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
GSK3640254 PK sampling			X				X	X	X	D8	X				X	X	X	X		Blood collection for PK analysis will be collected within 40 minutes prior to dosing on Days 1, 5, 6, and 7. Day 7 post-dose samples will be collected at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours.
Moxifloxacin PK sampling									X	D8							X	X		Blood collection for PK analysis of moxifloxacin will be collected within 40 minutes prior to the dose on Day 7. Day 7 post-dose samples will be collected at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours.
AE review			←==========X==========→																	
SAE review	←==========X==========→																			
Concomitant medication review	←==========X==========→																			

AE = adverse event; D = day; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; W = washout.

1. Participants may be furloughed during the washout portion of the respective period following Day 8 procedures after discussion with and approval of the investigator. If participants are furloughed during the washout period, they should return to the clinic on Day 14 for scheduled assessments prior to initiating the next period.
2. Evaluations scheduled for Day 9 of Period 4 will also be performed for participants who discontinue early.
3. Holter ECG recordings:
   - On Day -1 (Baseline), continuous ECG recordings (Holter) will be extracted at the following time points (relative to the time of planned dosing on the next day): pre-dose at -45, -30, and -15 minutes, and then after the time of planned dosing at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours.
   - On Day 1 of each period, continuous ECG recordings (Holter) will be performed starting approximately 2 hours before dosing and digital 12-lead ECGs will be extracted in replicates at -45, -30, and -15 minutes prior to dosing.
   - On Day 7 of each period, continuous ECG recordings (Holter) will be performed starting approximately 2 hours before dosing and digital 12-lead ECGs will be extracted in replicates at pre-dose (single time point), and then at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours after dosing.

- The timing and number of planned study assessments, including safety, pharmacokinetic (PK), or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging PK data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the competent authorities and the ethics committee before implementation.

2. INTRODUCTION

2.1. Study Rationale

The International Council for Harmonisation (ICH) E14 guidance, as adopted in the US Food and Drug Administration (FDA) Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs [DHHS, 2005], emphasizes the need to obtain clear and robust data through "thorough" studies that assess the effect of new chemical entities on electrocardiogram (ECG) parameters. Specifically, "thorough" studies are defined as trials dedicated to evaluating a compound's effect on cardiac repolarization, as measured by the corrected QT interval (QTc). Although many Phase 1, 2, and 3 studies may be conducted with a new compound, they typically utilize insufficient sample sizes, infrequent sampling of ECG data, or inadequate controls to overcome high variance in cardiac repolarization due to spontaneous change. Therefore, this thorough QT (TQT)/QTc study will be conducted to evaluate the effect of GSK3640254 on cardiac repolarization.

2.2. Background

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

At the time of this protocol submission, GSK has completed a Phase 2a study (short-term, monotherapy, proof of concept) on GSK3640254. Additionally, the safety, tolerability, and PK have been evaluated in 7 other completed Phase 1 studies in healthy volunteers up to a maximum dose of 320 mg daily for 14 days. The totality of the clinical data shows: 1) GSK3640254 is generally well-tolerated in short-term studies, and 2) GSK3640254 has a short-term PK/PD (decline in HIV-1 RNA) relationship. Summaries of the preclinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline (GSK) Document Number 2018N379610_01, 2019].

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

Previously, ViiV Healthcare (VH) studied a structurally similar MI, GSK3532795, in the Phase 2b study, Study 205891 (maximum dose 180 mg daily). The Week 24 primary endpoint analysis showed GSK3532795 was not optimal for Phase 3 development due to gastrointestinal (GI) intolerability and treatment-emergent resistance. Specifically, a relatively higher rate of GI intolerability (predominately Grade 1 to 2 diarrhoea in 38% to 61% of participants and abdominal pain in 8% to 22% of participants) and higher rate of nucleoside reverse transcriptase inhibitor resistance (6.5%) with clinically significant changes in GSK3532795 susceptibility were observed across all three GSK3532795

treatment arms [Morales-Ramirez, 2018]. Given these clinical and tolerability issues, the sponsor terminated Study 205891 and did not advance GSK3532795 into Phase 3 studies.

Aside from mild to moderate GI intolerability, 2 serious adverse events (SAEs) occurred in the Phase 1 TQT study AI468044/206220 [Bristol-Myers Squibb, 2017] at supratherapeutic doses: 1 healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The 2 participants received GSK3532795 at 240 mg twice daily (BID) and 240 mg once daily (QD) with food, respectively. These events were assessed as related to study drug but were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric adverse events (AEs) in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia, abnormal dreams).

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

2.2.2. Preclinical Summary with GSK3640254

2.2.2.1. Pharmacokinetics and Product Metabolism in Animals

Following intravenous administration, GSK3640254 exhibited low systemic clearance, high volume distribution, and elimination half-lives of 5.06, 4.0, 18.7, and 5.3 hours in mouse, rats, dogs and monkeys, respectively. GSK3640254 was eliminated mainly by direct glucuronidation followed by biliary excretion in bile-duct cannulated rats. Following repeat oral administration in the rat and dog, increases in systemic exposure to GSK3640254 was generally sub-proportional with dose. There was no or minimal accumulation of GSK3640254 after repeat dosing, and no consistent indication of a difference in exposure between genders. Metabolic pathways observed in vitro included mono-oxidation, N-dealkylation, and direct glucuronidation, with no unique metabolites generated in human liver microsomes or hepatocytes. In rat and dog plasma, GSK3640254 was either the only or the predominant drug-related component with minor oxidative metabolites.

Based on the predicted systemic exposures in humans, there is a potential risk for GSK3640254 to act as a perpetrator of drug-drug interactions (DDIs) of substrates of organic anion-transporting polypeptide 1B3 and multi-drug resistance protein 2. GSK3640254 was an inhibitor of uridine diphosphate glucuronosyltransferase (UGT) 1A1 and clinical DDI via this mechanism could be possible.

2.2.2.2. Toxicology in Animals

The primary target organ of toxicity in non-clinical studies with GSK3640254 was the stomach, with microscopic changes affecting parietal and chief cells in both rats and dogs. Due to microscopic changes in the stomach of rats at the lowest dose tested after 26 weeks, a no observed adverse effect level (NOAEL) in rats was unable to be determined. Microscopic findings in the stomach of rats were minimal to mild at the lowest observed adverse effect level (LOAEL) of 10 mg/kg/day (area under the plasma concentration-time curve [AUC] = 18.9 µg.hr/mL), corresponding to 0.63-fold the

measured highest mean human exposure in the planned Phase 2b clinical study. Following 39 weeks of dosing in dogs, the NOAEL for microscopic changes in the stomach was 0.2 mg/kg/day, and exposures were 0.28-fold the highest mean clinical exposure. Microscopic stomach changes were associated with increases in serum gastrin when evaluated in the 26- and 39-week studies in rats and dogs, respectively. All microscopic findings in the stomach of rats and dogs and changes in serum gastrin were shown to be partially reversible following a 4-week recovery period. Microscopic findings in the stomach were minimal to mild at the LOAELs of 10 mg/kg/day (AUC = 18.9 μg.hr/mL) and 1 mg/kg/day (AUC = 46.4 μg/hr/mL) in rats and dogs, respectively, corresponding to 0.63-fold and 1.6-fold highest mean clinical exposure in the planned Phase 2b clinical study. Potential effects in the stomach of humans during clinical studies are being investigated in a gastric safety sub-study.

With correction for protein binding, compared to the half maximal inhibitory concentration for the hERG/IKr potassium channel, there is a 7.9-fold margin above the predicted average clinical maximum observed concentration (Cmax) exposure for the highest dose planned in this study. Exposure where a minimal increase in QT interval was seen in a single dog in the single dose safety pharmacology study in telemeterized dogs was 1.8-fold higher than the predicted Cmax at the highest planned dose in this study. In addition, there were no effects on ECG parameters in dogs given up to 25 mg/kg/day for 4 weeks at 9.75-fold above the predicted average Cmax at the highest dose in this study.

2.2.3. Summary of GSK3640254 Clinical Pharmacokinetics

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

- Following single oral doses from 1 to 700 mg, AUC from time zero extrapolated to infinity, and Cmax tended to increase in a dose-proportional manner through 100 mg. Higher doses showed a less than dose-proportional increase in exposure and there was no apparent increase in exposure from 400 to 700 mg.

- 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 28 hours.

    - There was a slightly less than dose-proportional increase in Cmax and 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) was modest, and ranged from 8% to 50%.

- Coadministration with food increases overall GSK3640254 exposure 2- to 4-fold; therefore, GSK3640254 is recommended to be taken with food.

- There was no clinically meaningful drug interaction between GSK3640254 and either tenofovir alafenamide/emtricitabine (Study 208134) or dolutegravir (Study 209712).

Additional information regarding clinical PK data can be found in the CIB [GSK Document Number 2018N379610_01, 2019].

2.2.4. 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 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, 2019].

2.2.5. Summary of GSK3640254 Safety

A summary of safety data from 7 Phase 1 studies and a Phase 2a study performed to date is summarized below:

- No deaths or treatment-related SAEs have been reported during clinical studies with GSK3640254.

- The majority of AEs were CCI (Grade 1).

- Treatment-related dermatologic AEs (including AEs leading to study discontinuation) included rash, drug eruption, pruritis, urticaria, and maculopapular rash. Adverse events of urticaria and maculopapular rash led to discontinuation.

- Treatment emergent drug-related Grade 2 AEs included the following: headache (2 participants; one participant each in Studies 207187 and 208132), nausea (2 participants; one participant each in Studies 208134 and 208132), and abdominal pain (1 participant in Study 208132).

- Clinically notable AEs of elevated transaminases occurred in Studies 207187 (SAD/MAD, n = 1 healthy participant [17%], Grade 1) and 208135 (DDI with oral contraceptive Portia [ethinyl estradiol/levonorgestrel], n = 8 healthy participants [35%], 3 Grade 1 and 5 Grade 2). Subsequent analysis in Study 208135 showed no PK/PD relationship with either GSK3640254 or Portia and elevated transaminases. The elevated transaminases were likely due to the recent initiation of hormonal contraception in study participants.

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

- Across studies, the most common AEs regardless of grade, relationship, and concomitant medication administration were headache (11.9%), contact dermatitis and related events (7.8%), diarrhoea (5.5%), and abdominal pain (4.1%).

- Across studies, low grade GI intolerability has been observed; the majority were mild. Both Study 207187 (SAD/MAD) and Study 208312 (proof of concept) are relevant to this study given dosing of 7 to 14 days; most AEs in Study 207187 were unrelated and most AEs in Study 208132 were related.

- Across studies, there were generally no clinically significant changes in vital sign measurements, ECG results, or safety laboratory parameters (other than the elevated transaminases due to Portia, noted above). Specifically, no participant has demonstrated QT prolongation: absolute value >500 ms, or increase from baseline >60 ms.

The full safety profile for GSK3640254 can be found in the CIB [GSK Document Number 2018N379610_01, 2019].

2.2.5.1. 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 (C-QTc) analysis, a final model with a treatment effect-specific intercept reasonably represented the data. The slope of the C-QTc relationship was 0.004 ms per ng/mL (90% confidence interval [CI]: 0.0023 to 0.0048) with a small treatment effect-specific intercept of -0.9 ms (90% CI: -4.47 to 2.69). The QT effect (placebo-corrected change from baseline in QTcF [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 C-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).

2.3. Benefit/Risk Assessment

Based upon preclinical and clinical studies (including the prior MI GSK3532795), the potential risks for GSK3640254 are GI intolerability (e.g., abdominal pain and diarrhoea) and gastric toxicity (effects on parietal cell and chief cells), prolongation of QTc, neuropsychiatric safety, and rash.

Gastrointestinal intolerability will be assessed using clinical monitoring as outlined in Section 8.2.6.

Prolongation of the QTc interval is a risk. One preclinical study showed 1 dog with an increased QTc interval when given a single dose of GSK3640254. A cardiodynamic analysis of healthy participants in Study 207187 was conducted and summarized in Section 2.2.5.1. Importantly, in GSK3640254 clinical studies to date, there have been no abnormal clinically significant arrhythmias, and no participants met the study-based QTc stopping criteria for QTcF prolongations: values >500 ms or increases >60 ms from baseline. This study contains specific cardiac exclusion criteria (Section 5.2), has ECG monitoring (at Tmax once GSK3640254 attains steady state concentration [Section 1.3]), and has QTcF-based stopping criteria (Section 7.1.2).

Given the risk of psychiatric events as seen with GSK3532795 (Section 2.2.1), the protocol will exclude potential participants with any significant pre-existing psychiatric condition or positive (abnormal) response on the Columbia-Suicide Severity Rating Scale (C-SSRS; Section 5.2). Participants will also be required to provide response to the C-SSRS during the on-treatment portion of the study and will be clinically evaluated for suicidality as indicated (Section 1.3 and Section 8.2.5).

Across clinical studies, AEs leading to discontinuation have included urticaria and maculopapular rash. This study includes individual participant stopping criteria for any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement or any allergic or hypersensitivity reactions (Section 7.1.4).

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, neuropsychiatric safety, and rash), this clinical 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, 2019].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Preclinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with complementary DNA 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 (NOAEL) 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 2.2.5.1, 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, screening 24-hour Holter monitor, and cardiac medical history. **On-Treatment:** Participants will have safety 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).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 studies.	**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 intolerability 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 (MI) GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) were seen at supratherapeutic doses in healthy participants in the TQT study. From a neurologic and psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies, Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and Phase 2b studies). No exposure-response relationship was seen for select neurologic and psychiatric AEs (based on TQT and Phase 2b studies). Central nervous system penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. No clinical trends in the system organ class of neurologic or psychiatric AEs have been observed across the Phase 1 to 2a clinical studies.	**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. **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. Participants will also provide responses to the C-SSRS throughout the study. Ultimately, in the event of a new onset suicidality ideation or behaviour, as determined by the investigator (in consultation with psychiatry, as needed), the participant will discontinue from the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		study 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 studies, AEs leading to discontinuation have included urticaria and maculopapular rash.	**Screening:** A physical examination, including skin assessment, will be performed at screening. **On-Treatment:** Participants will undergo continuous evaluation for AEs during their participation in the study supplemented by the use of physical examinations. Protocol includes individual participant stopping criteria (Section 7.1.4), including: • Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement. • Any allergic or hypersensitivity reactions.
Moxifloxacin		
GI and cardiovascular toxicity	Nausea and vomiting are the most common AEs associated with oral moxifloxacin administration. Other less common side effects include vasodilation, tachycardia, dizziness, and allergic reactions. The risk of side effects from a single dose of moxifloxacin 400 mg is estimated to be minimal.	**Screening:** Protocol exclusion criteria based on pre-existing GI pathology or baseline GI signs/symptoms and screening ECG parameters and cardiac medical history. **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). Safety ECG monitoring will be performed (at a clinically reasonable frequency) during the course of the study (see SoA, Section 1.3) Participants with a history of sensitivity to moxifloxacin are excluded from the study.

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 are low, evaluable, and manageable.

Moxifloxacin is commonly used in clinical practice and has a well-characterized and acceptable safety profile. Given that only healthy participants will be enrolled and that participants will be confined to a clinical facility after dosing, 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.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	Primary
Part 1: • To determine the safety and pharmacokinetics of a supratherapeutic dose of GSK3640254 administered for 7 days in healthy participants	Part 1: • Area under the plasma concentration-time curve from time zero to time t (AUC[0-t]), area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state (AUC[0-τ]), maximum observed concentration (Cmax), plasma concentration at the end of the dosing interval (Cτ), and time of maximum observed concentration (Tmax) of GSK3640254 in plasma • Remaining Plasma will be analyzed for compound related metabolites • Safety and tolerability parameters for adverse events (AEs)/serious adverse events (SAEs), observed and change from baseline in clinical laboratory assessments, electrocardiograms (ECGs), and vital sign measurements
Part 2: • To determine the effect of therapeutic and supratherapeutic concentrations of multiple doses GSK3640254 on the QT interval corrected with Fridericia's formula (QTcF) in healthy participants	Part 2: • Placebo-corrected change from baseline in QTcF (ΔΔQTcF) for GSK3640254 using concentration-QTc (C-QTc) analysis (primary analysis) • Remaining Plasma will be analyzed for compound related metabolites

Objectives	Endpoints
Secondary	Secondary
Part 2: • To evaluate the effect of multiple oral therapeutic and supratherapeutic doses of GSK3640254 on other ECG parameters (heart rate [HR], PR, QRS, and QTcF intervals, treatment-emergent T-wave morphology, and appearance of U-waves)	Part 2: • Change from baseline in HR, QTcF, PR, QRS (ΔHR, ΔQTcF, ΔPR, and ΔQRS) intervals using by-time point analysis (secondary analysis); the placebo-corrected change from baseline in HR, PR, QTcF, and QRS (ΔΔHR, ΔΔPR, ΔΔQTcF, and ΔΔQRS) using by-timepoint analysis; categorical outliers for QTcF, HR, PR, and QRS; and the frequency of treatment emergent changes of T-wave morphology and U-wave presence
• To demonstrate assay sensitivity of the study design to detect a QTc effect using a single 400 mg oral moxifloxacin as a positive control.	• ΔΔQTcF for moxifloxacin (primary: C-QTc analysis and secondary: by-time point analysis)
• To evaluate the pharmacokinetics of multiple oral therapeutic and supratherapeutic doses of GSK3640254 and a single dose of moxifloxacin.	• AUC(0-t), AUC(0-τ), Cmax, Cτ, and Tmax of GSK3640254 in plasma • Cmax and Tmax of moxifloxacin in plasma
• To assess the safety and tolerability of multiple therapeutic and supratherapeutic doses of GSK3640254	• Safety and tolerability parameters for AEs/SAEs, observed and change from baseline in clinical laboratory assessments, ECGs, and vital sign measurements

4. STUDY DESIGN

4.1. Overall Design

This study has an adaptive 2-part design, where projected doses will be identified and may be modified according to assessment of accrued data. Part 1 will consist of up to 2 sentinel cohorts to determine the supratherapeutic dose for Part 2, which will be the main QTc study.

Part 1, Sentinel Cohorts: Part 1 will be a randomized, double-blind study in up to 2 sequential cohorts of approximately 8 healthy participants each (3:1 ratio to receive GSK3640254 or placebo) to evaluate the safety, tolerability, and PK following multiple-dose administration of GSK3640254 for 7 days.

Part 1 of the study will consist of a screening period, a check-in visit, and a treatment period for each cohort conducted. The first cohort will evaluate QD dosing of GSK3640254 or placebo. On Day 1 of the treatment period, 8 participants will be randomly assigned in a 3:1 ratio to receive GSK3640254 500 mg or placebo. All doses of study intervention will be administered under fed conditions. The participants will fast overnight for at least 8 hours prior to breakfast before the morning dose and will receive a moderate-fat meal (defined as approximately 600 calories, 30% from fat) 30 minutes prior to dosing. Participants will eat this meal within 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

The second cohort would evaluate BID dosing of GSK3640254. The second cohort would only be used if GSK3640254 PK or safety/tolerability endpoints defined above showed that an alternative supratherapeutic dose (other than 500 mg QD) would need to be evaluated in Part 2. The maximum dose for Cohort 2 will be 500 mg BID. The morning dose will be administered with a moderate-fat meal as previously described for Cohort 1. Participants will fast at least 2 hours prior to dinner before the evening dose. Participants will eat this meal within 25 minutes or less and dose administration will occur within 5 minutes of completion of meal consumption.

Participants will receive 1 of the following treatments:

- Sentinel Cohort 1: GSK3640254 500 mg or placebo orally QD for 7 days.
- Sentinel Cohort 2 (optional): If needed, a dose of GSK3540254 or placebo orally BID for 7 days (13 doses), with only a single morning dose administered on the seventh day. The specific dose in sentinel Cohort 2 will be determined based on the results of preliminary safety and PK data from sentinel Cohort 1 and decided upon by the study team and the investigator. Written confirmation of the dose decision for sentinel Cohort 2 will be provided to the IRB.

Pharmacokinetic blood samples for the analysis of GSK3640254 will be collected at selected time points pre-dose and up to 48 hours after the Day 7 morning dose.

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

Study assessments will be performed as indicated in the SoA (Section 1.3). Study participants will be confined to the clinic from Day -1 until discharge on Day 9. The total duration of the study for a participant in Part 1, including screening, is 37 days.

Part 2, Main QTc Study: Part 2 will be a double-blind (to GSK3540254 or placebo only), randomized, placebo-controlled study to investigate the safety, tolerability, and PK of GSK3640254 doses on cardiac conduction as compared to placebo and a single oral dose of moxifloxacin in healthy adult participants. Moxifloxacin is included as a positive control and will be open label. Approximately 42 participants will be randomized to ensure 34 evaluable participants with data from all treatment periods. Participants will be randomly assigned to 1 of 12 treatment sequences, with at least a 7-day washout after the final dose in each period. The supratherapeutic dose will be determined based on the results of preliminary safety and PK data from Part 1 and decided upon by the study team and the investigator.

All doses of study intervention will be administered under fed conditions. The participants will fast overnight for at least 8 hours prior to breakfast before the morning dose and will receive a moderate-fat meal (defined as approximately 600 calories, 30% from fat) 30 minutes prior to dosing. If participants will receive a BID dose, they will fast at least 2 hours prior to dinner before the evening dose. In both cases, participants will eat this meal within 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Part 2 of the study will consist of a screening period, a check-in visit (Day -2), a baseline visit (Day -1), and 4 sequential treatment periods. Prior to dosing on Day 1 of Period 1, participants will be randomly assigned to a treatment sequence.

Participants will receive treatments in 1 of the 12 following sequences:

Sequence	Period 1	Period 2	Period 3	Period 4
1	T	ST	P	M
2	ST	M	T	P
3	P	T	M	ST
4	M	P	ST	T
5	ST	P	T	M
6	P	M	ST	T
7	T	ST	M	P
8	M	T	P	ST
9	P	T	ST	M
10	T	M	P	ST
11	ST	P	M	T
12	M	ST	T	P

Treatment T: Therapeutic dose of GSK3640254 (100 mg once daily) Days 1 through 7.
Treatment ST: Supratherapeutic dose of GSK3640254 (to be determined from Part 1) Days 1 through 7.
Treatment P: Placebo for GSK3640254 Days 1 through 7.
Treatment M: Moxifloxacin; GSK3640254 placebo Days 1 through 6 and a single dose of Moxifloxacin (400 mg) on Day 7.
To maintain the blind, the number of tablets administered for therapeutic, supratherapeutic, (Days 1 through 6 only), and placebo doses will be identical. The total number of tablets will be based on the actual supratherapeutic dose derived from Part 1 of the study. For example, if the supratherapeutic dose is determined to be 500 mg QD, the therapeutic dose would consist of one 100 mg GSK3640254 tablet and four placebo tablets, the supratherapeutic dose would consist of five 100 mg GSK3640254 tablets, and the placebo dose would consist of five placebo tablets.

Continuous Holter ECG monitoring will be performed on Day -1 (full set of replicates mirroring pre- and post-dose time points). In each treatment period, continuous Holter ECG monitoring will be performed pre-dose on Day 1, and pre-dose and up to 24 hours after dosing on Day 7.

Pharmacokinetic blood samples for the analysis of GSK3640254 and moxifloxacin will be collected at selected time points pre-dose and up to 24 hours after the Day 7 morning dose.

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

Study assessments will be performed as indicated in the SoA (Section 1.3). Study participants will be confined to the clinic starting on Day -2 of Period 1. Final discharge will be on Day 9 of Period 4. The total duration of the study for a participant in Part 2, including screening, is approximately 82 days.

4.2. Scientific Rationale for Study Design

The purpose of this study is to provide an assessment of the effects of GSK3640254 on the QT interval. The design of the study follows the general design principles outlined in

the E14 guidance for the clinical evaluation of the QT/QTc with non-antiarrhythmic drugs [DHHS, 2005]. Both a therapeutic dose and a supratherapeutic dose of GSK3640254 will be evaluated in the main QTc study. As the supratherapeutic dose of GSK3640254 has not been determined, this study will be conducted as an adaptive 2-part design, where projected doses will be identified and may be modified according to assessment of accrued data. In Part 1, a sentinel cohort will be used to determine the supratherapeutic dose. If needed, a second sentinel cohort employing BID dosing may be added.

In accordance with ICH E14, this study will be conducted in healthy participants to eliminate variables known to influence ECG parameters (e.g., concomitant medications or diseases). The sample size will accommodate a time-matched statistical analysis on the primary endpoint, and a positive-control group will be utilized to establish assay sensitivity. Further, the half-life of GSK3640254 (i.e., 22 to 28 hours) allows for a crossover design, wherein the participants will act as their own controls.

As outlined in the ICH E14 guideline, the study will use a randomized, partially double-blind (open label for moxifloxacin), placebo- and positive-controlled design. The positive control, moxifloxacin, will be used to confirm assay sensitivity for QTc prolongation. Moxifloxacin is a widely used positive reference substance for assaying the sensitivity of a TQT study to detect changes in the QTc interval at a single dose of 400 mg.

GSK3640254 will be administered under double-blind conditions to avoid bias. The central ECG laboratory will be blinded to dose consistent with FDA standards.

4.3. Justification for Dose

A single dose of GSK3640254 will likely not be able to achieve therapeutic or supratherapeutic exposures; thus, multiple-dose administration will be needed. A projected therapeutic dose of 100 mg GSK3640254 was selected for this study (the dose range in a planned Phase 2b dose range finding study in HIV-1 infected adults is 100 to 200 mg QD). The initial planned dose for Part 1 was selected based on a population PK model referenced on the single-dose (1 to 400 mg) and multiple-dose (50 to 320 mg QD for 14 days) data from healthy participants from the FTIH study 207187, as well as the multiple-dose data in HIV-1 infected participants (10 to 200 mg QD for 7 to 10 days). The PK of GSK3640254 (given with food) was described by a two-compartment model with sequential zero-order absorption (in the depot compartment) followed by first order absorption (from depot to the central compartment) and first order elimination. Weight was found to be a significant covariate on Ka. In addition, study (as a surrogate for subject type and differences in GSK3640254 salt formulations between the 2 studies) was also found to be significant covariates on bioavailability (F was ~27% lower in the FTIH Study 207187 compared to that from the proof of concept Study 208132).

As indicated in Section 4.2, the supratherapeutic dose of GSK3640254 has not been determined. The target supratherapeutic exposure (steady-state Cmax) is approximately 4.4 µg/mL, which provides approximately 4-fold cover for 100 mg QD therapeutic dose, 2-fold for 200 mg QD, 1:1 for inhibitors with a 200 mg dose or 2:1 with 100 mg dose (assuming an increase in exposure with CYP-inhibitors of approximately 2-fold).

This study will be conducted as an adaptive 2-part design, where projected supratherapeutic doses will be identified and may be modified according to assessment of accrued data. In Part 1, a sentinel cohort will be used to determine whether 500 mg QD elicits the target supratherapeutic exposure as predicted by the population PK model, and assuming dose linearity. The requirement to conduct sentinel Cohort 2 in Part 1 will be determined based on the results of preliminary safety and PK data from sentinel Cohort 1 and decided upon by the study team and investigator. Cohort 2 (where a BID dosing regimen would be evaluated not to exceed 500 mg BID) will be conducted only if the 500 mg QD evaluated in Cohort 1 fails to result in approximately c µg/mL at steady state. In Part 2, the supratherapeutic dose will represent a dose that is equal to or less than the highest total dose that was evaluated in the sentinel cohorts.

Written confirmation of the decision to conduct sentinel Cohort 2 (Part 1) and the supratherapeutic dose for QTc evaluation (Part 2) will be provided to the investigator, and the IRB will be notified for informational purposes only

4.4. End of Study Definition

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

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

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. Efforts will be made to recruit at least 30% of each gender.

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 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, planning to become pregnant within the next 6 months, 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 non-hormonal 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.
      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 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), 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 (prior appendectomy is acceptable).
4. Clinically significant illness, including viral syndromes, within 3 weeks of dosing.
5. 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 (World Health Organization [WHO] definitions, Section 10.7.3.2.1).
6. Any history of significant underlying psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder with or without psychotic symptoms, other psychotic disorders, or schizotypal (personality) disorder.
7. Any history of major depressive disorder with or without suicidal features, or anxiety disorders that required medical intervention (pharmacologic or not) such as hospitalization or other inpatient treatment and/or chronic (>6 months) outpatient treatment. Participants with other conditions such as adjustment disorder or dysthymia that have required shorter term medical therapy (<6 months) without inpatient treatment and are currently well-controlled clinically or resolved may be considered for entry after discussion and agreement with the VH/GSK Medical Monitor.
8. Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the investigator (with or without psychiatric evaluation), could interfere with the participant's ability to comply with the dosing schedule and protocol evaluations or which might compromise the safety of the participant.
9. 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.
10. History indicative of an increased risk of a cardiac arrhythmia or cardiac disease, including the following:
    a. History of symptomatic cardiac arrhythmias or palpitations associated with presyncope or syncope, or history of unexplained syncope.
    b. History of cardiac arrest.
    c. 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 (HR) 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).

d. History of clinically relevant structural cardiac disease including hypertrophic obstructive cardiomyopathy.

e. History of hypokalemia.

11. History of heart disease (e.g., coronary heart disease, angina).

Laboratory Assessments

12. Presence of hepatitis B surface antigen at Screening or within 3 months prior to starting study intervention.
13. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention.
14. Positive HIV-1 and -2 antigen/antibody immunoassay at Screening.
15. 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.
16. 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.
17. Any acute laboratory abnormality (including hypokalemia, hypercalcemia, or hypomagnesemia) at Screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
18. Any Grade 2 to 4 laboratory abnormality at Screening, with the exception of lipid abnormalities (e.g., total cholesterol, triglycerides), and ALT (previously described), 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.
19. Urine drug screen positive (showing presence of): amphetamines, barbiturates, cocaine, MDMA, cannabinoids, methamphetamines, phencyclidine, or non-prescribed opiates, oxycodone, benzodiazepines, methadone, or tricyclic antidepressants at screening or before dosing of study intervention.

Prior/Concomitant Therapy

20. 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.)
21. Treatment with any vaccine within 30 days prior to receiving study intervention.

22. Unwillingness to abstain from 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

23. 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).
24. Prior exposure to GSK3640254 in this or another clinical study.
25. Prior intolerance to moxifloxacin.
26. Prior participation in this clinical study (i.e., participants may not participate in both Part 1 and Part 2 of the 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. A sustained supine systolic blood pressure >150 mm Hg or <90 mm Hg or a supine diastolic blood pressure >95 mm Hg or <50 mm Hg at Screening or Check-in (Day -2). Blood pressure may be retested once in the supine position. The blood pressure abnormality is considered sustained if either the systolic or the diastolic pressure values are outside the stated limits after 2 assessments, in which case the participant may not be randomized.
30. A resting HR of <50 bpm or >100 bpm when vital signs are measured at Screening or Check-in (Day -2). A HR from 100 to 110 bpm can be rechecked by ECG or vital signs within up to 2 hours to verify eligibility.
31. An uninterpretable ECG or any significant arrhythmia or ECG finding (e.g., prior myocardial infarction in the past 3 months, significant pathological Q-waves [defined as Q-wave >40 ms or depth greater than 0.4-0.5 mV], symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, ventricular pre-excitation, non-sustained or sustained ventricular tachycardia, any degree of atrioventricular block, complete left bundle branch block, or conduction abnormality) which, in the opinion of the investigator or VH/GSK Medical Monitor, will interfere with the safety of the individual participant.

32. Exclusion criteria for Screening ECG (a single repeat is allowed for eligibility determination):

HR	<50 or >100 bpm
QTcF interval[1]	>450 ms
QRS interval	>110 ms
PR interval	>200 ms

1. The QTc is the QT interval corrected for HR 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. The Investigator's or ViiV Medical Monitor's over-read can supersede that of the machine at any time.

33. Screening Holter (24 hours) with any of the following:

- Sinus bradycardia ≤35 bpm or junctional arrhythmia >60 bpm for 10 seconds or longer.
- Non-sustained ventricular tachycardia or more than 30 ventricular premature depolarizations during an hour.
- Atrial arrhythmia >100 bpm for 3 seconds or longer or more than 40 atrial premature depolarizations during an hour.

Other Exclusions

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

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants will abstain from consumption of 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.
- The participants will fast overnight for at least 8 hours prior to dosing and will be provided a breakfast 30 minutes prior to morning 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 7 of each period). The moderate-fat meal will contain about 600 calories with approximately 30% of the calories coming from fat.

- A standard lunch will be provided 4 hours after morning dosing. A standard dinner will be served approximately 10 hours after morning dosing. Participants will eat this meal in 25 minutes or less. Evening dose administration (if needed for BID dosing) will occur within 5 minutes of completion of meal consumption. A snack may be provided approximately 13 hours after morning dosing. The overnight fast will start after the evening snack (within at least 8 hours relative to the morning dose on the following day). The food content of meals must be identical on serial ECG and PK sampling days (i.e., Day 7 of each period).
- No water is allowed from 1 hour prior to dosing until 1 hour after dosing except for the glass of water needed to administer the study intervention (e.g., 240 mL). Water is allowed ad libitum at all other times. 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.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, energy drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 48 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco- and nicotine-containing products will not be allowed from 3 months prior to Screening until after the final visit.
- Participants must have a negative drug test at Screening and Check-in 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 96 hours (4 days) prior to entry into the clinic on Day -1 (Part 1) or Day -2 (Part 2) and throughout the study.
- In Part 2, participants should refrain from activities or conversations leading to increased stimulation during the serial ECG collection period (approximately 1 hour before dosing on Day 1 and up to 24 hours after the morning dose on Day 7). During serial ECG sampling, participants will not be allowed to have electronic devices (e.g., cellular telephone, tablet, computer) or watch television.
- In Part 2, participants should maintain a supine position for at least 1.5 hours before dosing and for the first 4 hours after dosing except for study intervention administration. At all other serial ECG time points, participants are required to remain in the supine position for at least 15 minutes prior and 10 minutes after the nominal ECG time point.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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) should not be rescreened.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

Intervention Name	**GSK3640254**	**GSK3640254 Placebo**	**Moxifloxacin**
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Capsule
Unit Dose Strength	100 mg	N/A	400 mg
Dosage Levels	Therapeutic: 100 mg Supratherapeutic: TBD	N/A	400 mg
Route of Administration	Oral	Oral	Oral
IMP and NIMP	IMP	IMP	IMP
Sourcing	Sponsor	Sponsor	Investigator
Packaging and Labeling	Provided in bulk by GSK. The investigator will package in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.	Provided in bulk by GSK. 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; TBD = to be determined.

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 labelled 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 a partially double-blind study (moxifloxacin is open label in Part 2). Study participants will be randomly assigned to a treatment (Part 1) or treatment sequence (Part 2) in accordance with the randomization schedule generated by PPD prior to the start of the study and using validated software. On Period 1 Day 1 (both Part 1 and Part 2), participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to study intervention, according to the randomization schedule. Each participant will be dispensed blinded study intervention (open label for moxifloxacin), labelled with his or her unique randomization number throughout the study.

Participants will be randomly assigned to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention (GSK3640254 or placebo) throughout the course of the study. In order to maintain this blind, an unblinded pharmacist will be responsible for the reconstitution and preparation of GSK3640254 or placebo and will endeavour to ensure there are no differences in time taken to dispense study intervention following randomization. Unblinded monitors and the auditor(s), in the event of a quality assurance audit, will be allowed access to unblinded study intervention records at the site to verify that randomization/dispensing have been performed accurately.

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

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

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 CRF. Other medications are not permitted without prior discussion with the VH/GSK Medical Monitor.

6.6. Dose Modification

In Part 1, each participant in sentinel Cohort 1 will be administered GSK3640254 500 mg or placebo QD for 7 days. If sentinel Cohort 2 is needed, it is planned that each participant will be administered GSK3640254 or placebo BID for 7 days, with only a single morning dose administered on the seventh day. The decision to proceed to sentinel Cohort 2 and the actual dose of GSK3640254 (either an increase or a decrease) will be made by the study team and the investigator based on preliminary safety and PK data from Cohort 1. Written confirmation of proceeding to sentinel Cohort 2 will be provided to the IRB for informational purposes only

In Part 2, the main QTc study, the therapeutic dose of GSK3640254 will be 100 mg QD for 7 days. The supratherapeutic dose will be determined based on the results of preliminary safety and PK data from the sentinel cohort(s). The supratherapeutic dose will represent a dose that is equal to or less than the highest total dose that was evaluated in the sentinel cohort(s). Written confirmation of the dose decision for the supratherapeutic dose for QTc evaluation (Part 2) will be provided to the investigator and the IRB will be notified for informational purposes only

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from VH/GSK or with GSK3640254 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 and follow-up and for any further evaluations that need to be completed.

7.1.1. Phase 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 FDA premarketing clinical liver safety guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf).

Discontinuation of study intervention for abnormal liver tests is required when a participant has an ALT ≥3 × ULN or when, in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

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.

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

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

7.1.2. Safety ECG 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 intra-period pre-dose Day 1 time point ECGs will generate a triplicate averaged QTcF (over a brief approximately 5 to 10 minute recording period). This pre-dose triplicate averaged QTcF value will serve as the baseline for the applicable study period. For example, in Period 1, the pre-dose triplicate ECGs on Day 1 will serve as the basis for the baseline QTcF for Period 1 only.
- A randomized participant who 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 the following: 1) a complete unscheduled chemistry panel, 2) an unscheduled GSK3640254 PK sample and 3) repeated unscheduled ECGs until their QTcF measurement returns to their original averaged QTcF value at intra-period Day 1 pre-dose.

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 Criteria

Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered C-SSRS during the treatment phase of the study 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
- A participant must permanently discontinue study intervention and be discontinued from the study if they have COVID-19 infection as clinically determined by the investigator (suspected, probable, or confirmed using the most recent version of the WHO case definition. Note: if this occurs, all other participants within the same cohort as the participant who developed COVID-19 infection will be discharged from the site regardless of whether or not they are symptomatic.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, 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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded 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, forehead, or tympanic temperature; pulse rate; respiratory rate; and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-recumbent or supine position with a completely automated device. The site will follow their standard process for repeating vital signs, as needed.

- 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.

8.2.3. Safety Electrocardiograms

- Twelve-lead ECGs will be obtained using an ECG machine that automatically calculates the HR 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 available 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 Behaviour 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. Repeat assessments will be performed during the treatment phase of the study. In case of a 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 Intolerability Evaluation and Monitoring Plan (with Stopping Criteria)

Preclinical toxicology studies in rats and dogs have suggested a potential for GI related toxicity with GSK3640254.

Prior clinical trials have not evaluated for the presence of gastric toxicity in humans. Thus, it is unclear if any of the GI AEs observed in any clinical trial were representative of, associated with, or resulted from gastric toxicity (if present). 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 may 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 gastrointestinal (GI) clinical syndromes that may occur (possibly in combination) during the clinical study.**
Abdominal Pain	The investigator should obtain information on chronology, location, intensity/character, aggravating and alleviating factors, and associated symptoms in the context of the participants' relevant past medical history [Millham, 2016]. With chronic symptoms, factors suggestive of an organic process include the following: fever, night sweats, loss of appetite, weight loss, and nocturnal awakening [Yarze, 2016]. The historical and physical examination should be efficient and lead to an accurate diagnosis soon after presentation.
Nausea and Vomiting	The investigator should attempt to identify the etiology of these symptoms (and whether they are 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 the following: pharyngitis, asthma, bronchitis, hoarseness, chest pain, or abdominal pain.
Diarrhea	Similar to other GI symptoms, important historical assessment includes duration, onset, pattern, epidemiology (e.g. travel and diet), aggravating or iatrogenic factors, alleviating factors, stool appearance, presence of other symptoms (e.g., abdominal pain), or weight loss. The differential can be narrowed if there are clear watery, inflammatory, or fatty manifestations [Schiller, 2016].
Other Clinical Syndromes	Additional diagnostic criteria for other GI disorders potentially encountered in the clinical study are available elsewhere [Rome Foundation, 2019].
PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history [Hasler, 2012]. The examination elements may include the following: auscultation for bowel sounds (up to 2 minutes if necessary) and palpation (including assessment for rebound, guarding, and muscular rigidity [Millham, 2016]. Acutely, the investigator may assess for signs of intravascular volume depletion (e.g., orthostasis) and/or aspiration of vomitus as appropriate. Abdominal tenderness and guarding may indicate inflammation. The presence of fecal blood can indicate mucosal damage (e.g., from an ulcer). Complete evaluation of dyspepsia should include an oral examination (poor dentition or pharyngeal erythema) and lungs for wheezing.**
DIAGNOSTIC EVALUATION AND MANAGEMENT	**A major goal in the diagnostic evaluation of a participant with upper GI symptoms is to quickly arrive at a final diagnosis without exposing the participant to unnecessary (invasive) testing; investigators should exercise good clinical judgment in this regard [Soll, 2009]. A major goal of therapy is directed at correcting the underlying identifiable medical or**

	surgical abnormalities [e.g., perforation or infarction) [Malagelada, 2016]. Consultation (e.g., gastroenterologist) is recommended as clinically indicated. Emergent action should be taken as necessary: correction of hypovolemia or electrolyte abnormalities.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

8.2.7. COVID-19 Measures

The measures approved for implementation within this clinical trial to protect participant safety, welfare, and rights, and ensure data integrity and the integrity of the clinical trial, as a result of COVID-19 only, are outlined in Appendix 7.

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 at the time of the last participant last visit PPD 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 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 on 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 recording 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 an AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Participants will be questioned prior to each dose of study intervention.

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 non-serious 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, IRBs/IECs, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the CIB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

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

8.4. Treatment of Overdose

For this study, any dose of GSK3640254 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 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).
37. 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 and moxifloxacin as specified in the SoA (Section 1.3).
- 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 moxifloxacin. 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 analysed for GSK3640254 and moxifloxacin, any remaining plasma will be analysed for other compound-related metabolites and the results provided in a separate report.

8.6. Cardiodynamic Assessments

Not Applicable

8.6.1. Continuous Holter Electrocardiograms

Pre-dose digital 12-lead ECGs will be extracted in replicates from continuous Holter recordings. On Day -1 (Baseline), continuous Holter ECG recordings will be extracted at the following time points (relative to the time of planned dosing on the next day): pre-dose at -45, -30, and -15 minutes, and then after the time of planned dosing at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours. The Holter ECG should be started approximately 2 hours before dosing on Day 1 of each period, and ECG extractions will occur at -45, -30, and -15 minutes before dosing. On Day 7, 12-lead ECGs will be extracted from continuous Holter recordings pre-dose (single time point) and after the morning dose at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours in each period.

Electrocardiograms will be extracted from the continuous recording by a central ECG laboratory (ERT, Rochester, NY). The ECGs will be extracted from the continuous recording during an extraction window of 5 minutes prior to the nominal time point. Each ECG extraction window will be preceded by an approximate 15-minute supine rest period in an undisturbed environment.

The ECG extractions will be time-matched to the PK samples, but will be obtained before the actual PK sampling time to avoid changes in autonomic tone associated with the psychological aspects of blood collection as well as the reduction in blood volume subsequent to blood collection. When time points for assessments coincide, the order should be safety ECGs, vital signs, ECG extraction, and then PK blood collection.

The following ECG parameters will be measured and calculated: HR, PR interval, QTcF, QRS interval, T-wave morphology, and U-wave presence.

8.6.2. Cardiodynamic Sample Analysis

The primary analysis will be based on C-QTc modeling of the relationship between GSK3640254 plasma concentration and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of ΔΔQTcF >10 ms at clinically relevant plasma levels of GSK3640254.

In addition, the effect of GSK3640254 on placebo-corrected change-from-baseline in QTcF, HR, PR, and QRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) will be evaluated at each post-dose time point ("by-time point" analysis) using the intersection union test. An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence.

Assay sensitivity will be evaluated by C-QTc analysis of the effect on (ΔΔQTcF) of moxifloxacin using the same model as for the primary analysis. Assay sensitivity will be deemed met if the slope of the C-QTc relationship is statistically significant at the 10% level in a 2-sided test and the predicted QTc effect (i.e., the lower bound of the 2-sided 90% CI of ΔΔQTcF) is above 5 ms at the observed geometric mean Cmax of 400 mg moxifloxacin.

For all continuous ECG parameters from each period, baseline will be the average of the derived ECG intervals from the 3 ECG time points prior to dosing (-45, -30,

and -15 minutes) on Day 1 for the respective period. For T-wave morphology and U-wave presence, baseline includes any findings observed in any replicates from the 3 pre-dose time points (-45, -30, and -15 minutes) on Day 1 in each period.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal statistical hypothesis to be tested in Part 1.

For Part 2, the statistical hypothesis to be tested for the primary assessment of QT prolongation at the highest clinically relevant exposure using the C-QTc analysis for each active dose group is:
H_0: *ΔΔQTcF ≥10 ms*

H_1: *ΔΔQTcF <10 ms*

where ΔΔQTcF is the mean ΔΔQTcF at the mean Cmax for each active dose group, respectively.

In addition, the statistical hypothesis to be tested for the assay sensitivity using the C-QTc analysis is:

H_0: *ΔΔQTcF ≤5 ms*

H_1: *ΔΔQTcF >5 ms*

where ΔΔQTcF is the mean ΔΔQTcF at the mean Cmax for the moxifloxacin group.

9.2. Sample Size Determination

Part 1: A total of up to 16 participants are planned to be randomized, 8 participants per cohort (6 participants to receive GSK3640254 and 2 participants to receive placebo). For

Part 1, as there is no formal research hypothesis being statistically tested, the sample size is not selected based on statistical considerations but was determined using feasibility.

Part 2: A sample size of approximately 42 participants is chosen to obtain 34 evaluable participants to complete the study. A sample size of 34 evaluable participants will provide more than 90% power to exclude that active drug causes more than a 10-ms QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% CI of the model predicted QTc effect (ΔΔQTcF) at the observed geometric mean Cmax of active drug in the study.

This power is estimated approximately using a paired t-test. The calculation assumes a one-sided 5% significance level, an underlying effect of GSK3640254 of 4 ms and a standard deviation (SD) of the ΔQTc of 8.5 ms for both active drug and placebo. Table 2 provides the sample sizes for power of 90% and 95% with underlying effect of 3, 4, and 5 ms and SD of 8, 8.5, and 9.5 ms.

The C-QTc analysis method is supported by Darpo, 2015 and Ferber, 2015 and consistent with the experiences from 25 recent TQT studies in ERT, which provided SD=8 ms as a conservative estimate for general TQT studies. Note that this calculation is conservative also because it does not take into account any gain in precision due to the use of all data of each participant with the help of a linear mixed effects model. An SD of 9.5 ms is a conservative value used in previous MI compound BMS-663068 and AI compound Fostemsavir TQT studies in GSK. In the previous GSK3640254 FTIH Study 207187 SAD/MAD study, the within-participant SD based on by-time point analysis was 8.5 ms, which provides the conservative estimated SD for this compound. Therefore, the underlying effect 4 ms and SD=8.5 ms with 90% of power for the study sample size of 34 participants was chosen for this study. With the dropout rate of 20%, approximately 42 participants will be enrolled to ensure the evaluable number of participants is greater or equal to 34.

Table 2 Sample Size Determination - Power

Sample size	Number of Participants for 90% Power	Number of Participants for 95% Power
Underlying effect 3 ms SD = 8 ms	22	28
Underlying effect 3 ms SD = 8.5 ms	25	32
Underlying effect 3 ms SD = 9.5 ms	32	40
Underlying effect 4 ms SD = 8 ms	30	38
Underlying effect 4 ms SD = 8.5 ms	34	43
Underlying effect 4 ms, SD = 9.5 ms	43	54
Underlying effect 5 ms SD = 8 ms	44	55
Underlying effect 5 ms SD = 8.5 ms	49	63
Underlying effect 5 ms SD = 9.5 ms	62	78

Sample Size for Assay Sensitivity: To demonstrate assay sensitivity with C-QTc analysis, it must be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 ms (i.e., the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTcF] should exceed 5 ms).

In a similarly designed, recent crossover study with 24 healthy participants (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the C-QTc analysis was 1.24 ms. The within-subject SD of ΔQTcF in this study was 5.4 ms based on the by-time point analysis. If the effect of moxifloxacin is assumed to be 10 ms, the SE of 1.24 ms corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.62 required to guarantee a power of at least 95% in a paired *t*-test situation with a sample size of 30 evaluable participants. In other words, based on this calculation, a power of at least 95% for 30 evaluable participants will be obtained as long as the variability of the ΔQTcF, as measured by its within-subject SD, does not exceed 7.1 ms (i.e., 132% of the 5.4 ms observed in the above referenced study [on-file data, ERT]) assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD. The number also agrees with recent recommendations of the FDA, which propose at least 20 participants [Huang, 2019].

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Randomized	All participants who are randomly assigned to a treatment/treatment sequence.
Safety	All randomized participants who receive at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received. This population will be used for all demographic and safety summaries.
QT/QTc	The QT/QTc population will include all participants in the safety population with measurements at baseline as well as on-treatment with at least 1 post-dose time point with a valid ΔQTcF value. The QT/QTc population will be used for the by-time point assay sensitivity, and categorical analyses of the cardiodynamic ECG parameters.
PK 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.
PK 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 and summary tables.
PK/QTc	The PK/QTc Population will include all participants who are in both the QT/QTc and PK concentration populations with at least 1 pair of post-dose PK and QTcF data from the same time point as well as participants in the QT/QTc population who received placebo. The PK/QTc population will be used for the C-QTc analysis. The PK/QTc Population will be defined for GSK3640254 and for moxifloxacin.

9.4. Statistical Analyses

9.4.1. Cardiodynamic Analyses

9.4.1.1. QT Correction Methods

The QT and RR value for each beat will be used for HR correction. The primary HR correction method will be the Fridericia's correction (QTcF) defined as $QTcF\ (ms) = QT\ (ms)/[RR\ (ms)/1000]^{1/3}$ if there is no effect of GSK3640254 on HR.

If a substantial HR effect is observed (i.e., the largest least squares [LS] mean ΔΔHR is greater than 10 bpm in the by-time point analysis), other correction methods such as optimized HR-corrected QT interval (QTcI), and individual HR-corrected QT interval (QTcS) will be explored using the drug-free QT/RR data extracted from the full range of HR in the 24-hour Holter recording on Day -1. The method that removes the HR

dependence of the QT interval most efficiently will be chosen as the primary correction method. More details will be described in a separate statistical analysis plan.

9.4.1.2. Concentration-QTc Analysis (Primary Analysis)

The relationship between GSK3640254 plasma concentrations and ΔQTcF will be quantified using a linear mixed-effects modelling approach. The model will have ΔQTcF as the dependent variable, GSK3640254 plasma concentration as the exploratory variate (0 for placebo), centred baseline QTcF (i.e., baseline QTcF for individual participant minus the population mean baseline QTcF for all participants in the same treatment period) as an additional covariate, treatment (active = 1 or placebo = 0) and time (i.e., post-dose time point) as fixed effects, and random intercept and slope per participant [Garnett, 2018]. An unstructured covariance matrix will be specified for the random effects. If convergence cannot be achieved even after appropriate rescaling of the concentrations, the random effect on the slope and intercept will be dropped, in this order, until convergence is achieved. The degrees of freedom of estimates will be determined by the Kenward-Roger method. From the model, the slope (i.e., the regression parameter for concentration) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with the 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

The geometric mean of the individual Cmax values for participants in each of the active dose groups will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTcF (i.e., slope estimate × concentration + treatment effect-specific intercept) at this geometric mean Cmax of GSK3640254 will be obtained. If the upper bound of the 2-sided 90% CI of the predicted effect of ΔΔQTcF at clinically relevant plasma levels of GSK3640254 is below 10 ms, it will be concluded that GSK3640254 does not cause clinically relevant QTc prolongation.

The plot of the observed median-quantile GSK3640254 concentrations and associated mean placebo-adjusted ΔQTcF (i.e., ΔΔQTcF) with 2-sided 90% CI adjusted for diurnal effects, together with the regression line presenting the predicted ΔΔQTcF (2-sided 90% CI) [Tornøe, 2011] will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the C-QTc relationship. The observed ΔQTcF values from the active group will be adjusted by the estimated time effect from the C-QTc model (i.e., the estimated diurnal effect under the placebo treatment). The individually estimated placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for participant i administered GSK3640254 at time point j minus the estimation of time effect at time point j. For evaluation of the HR-corrected QT interval, a scatter plot and quantile plot of QTcF and RR intervals by treatment with regression line and a linear mixed-effects line (90% CI), respectively, will also be given. Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of cardiodynamic model (linear versus nonlinear) as follows.

Hysteresis will be assessed based on joint graphical displays of the LS mean difference between ΔQTcF under GSK3640254 and under placebo (ΔΔQTcF) for each post-dose time point from the by-time point analysis and the mean concentrations of GSK3640254

at the same time points. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 ms cannot be excluded in the by-time point analysis in the 2 active dose groups, and if the mean peak ΔΔQTcF effect is observed at the same time point in the by-time point analysis in the 2 active dose groups, and if a delay between peak ΔΔQTcF and peak plasma concentration in the plot (ΔΔQTcF versus GSK3640254) of more than 1 hour is observed in a consistent way for the 2 active dose groups, other C-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if the curve of the hysteresis plot shows a counterclockwise loop. A significant treatment effect-specific intercept is not biologically plausible and therefore may be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

To assess the appropriateness of a linear model, normal Q-Q plots for the standardized residuals and the random effects, and plots of standardized residuals versus concentration, fitted values, centered baseline QTcF, nominal time, and active treatment will be produced. Scatter plots for standard residuals versus continuous covariates and box plots for standard residuals versus discrete covariates will be provided. The scatter plots of standardized residuals versus concentration and versus centered baseline QTcF by LOESS fitting (i.e., locally weighted scatter plot smoothing as described by [Cleveland, 1979]) will also be produced with optimal smoothing parameters selected by the Akaike information criterion with a correction (AICC [Hurvich, 1998]). A scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear C-QTc relationship. If there is an indication that a linear model is inappropriate, additional models will be fitted, in particular an Emax model. The C-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

9.4.1.3. By-Time Point Analysis (Secondary Analysis)

The “by-time point analysis” for QTcF will be based on a linear mixed-effects model with ΔQTcF as the dependent variable, period, sequence, time (i.e., time point: categorical), treatment (GSK3640254, moxifloxacin, and placebo), and time-by-treatment interaction as fixed effects, and baseline QTcF as a covariate. An unstructured covariance matrix will be specified for the repeated measures at post-dose time points for participant within treatment period. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as autoregressive and compound symmetry will be considered. The model will also include a participant-specific random effect. If the fixed effects for period and/or sequence should prove to be not significant (that is, if the *p*-value >0.1), these effects may be removed from the model and the analysis will be repeated without those covariates. From this analysis, the LS mean and 2-sided 90% CI will be calculated for the contrast “GSK3640254 versus placebo” for each dose of GSK3640254 at each post-dose time point, separately.

For HR, PR, and QRS interval, the analysis will be based on the change-from-baseline post-dosing (ΔHR, ΔPR, and ΔQRS). The same (by-time point analysis) model will be used as described for QTcF. The LS mean, SE, and 2-sided 90% CI from the statistical

modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

9.4.1.4. Categorical Analysis

The analyses results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both number of participants and number of time points. For categorical outliers, the number (percentage) of participants as well as time points who had increases in absolute QTcF interval values >450 and ≤480 ms, >480 and ≤500 ms, and >500 ms, and changes from pre-dose baseline of >30 and ≤60 ms, and >60 ms; increase in PR interval from pre-dose baseline >25% to a PR >200 ms; increase in QRS interval from pre-dose baseline >25% to a QRS >120 ms; decrease in HR from pre-dose baseline >25% to a HR <50 bpm; and increase in HR from pre-dose baseline >25% to a HR >100 bpm will be determined.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the time point.

9.4.1.5. Assay Sensitivity

Assay sensitivity will be evaluated by C-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using the same model as for the primary analysis. If the slope of the moxifloxacin plasma concentration/ΔQTcF relationship is statistically significant at the 10% level in a 2-sided test and the lower bound of the 2-sided 90% CI of the predicted QTc effect at the geometric mean Cmax of the 400 mg dose is above 5 ms, assay sensitivity will be deemed to have been demonstrated.

9.4.2. Pharmacokinetic Analyses

Plasma GSK3640254 concentration-time data will be analysed by PPD, under the oversight of Clinical Pharmacology Modelling & 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	• For Part 1, 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: o AUC(0-t), AUC(0-τ), Cmax, Cτ, and Tmax • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 PK parameter values will be presented by treatment. • Additionally, pre-dose (trough) PK plasma concentrations of GSK3640254 will be summarized and used to assess achievement of steady state.

Endpoint	Statistical Analysis Methods
Secondary	• For Part 2, plasma concentrations of GSK3640254 and moxifloxacin 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: o Treatments T and ST: AUC(0-t), AUC(0-τ), Cmax, Cτ, and Tmax of GSK3640254 o Treatment M: Cmax and Tmax of moxifloxacin • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 and moxifloxacin PK parameter values will be presented. • Additionally, pre-dose (trough) PK plasma concentrations of GSK3640254 will be summarized and used to assess achievement of steady state.

9.4.3. 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 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.

9.4.4. Other Analysis

Special statistical and data analysis considerations may be warranted in the event that 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 reporting and analysis plan; alternatively, a separate reporting and analysis plan focusing on modified data handling rules (e.g., changes to analysis populations, visit windows and endpoints) and analyses (e.g., sensitivity analyses to assess impact of and account for missing data) may be prepared, taking in to account applicable regulatory guidance and industry best practices for handling such situations [DHHS, 2020; EMA, 2020a; EMA, 2020b].

9.5. Interim Analyses

After completion of the study Part 1 Cohort 1 (and Cohort 2 if conducted), preliminary safety & PK data based on nominal time will be analyzed by PPD as soon as PK data are available under the oversight of Clinical Pharmacology Modeling & Simulation within GSK; the data will be used to determine selection of the supratherapeutic dose to be used in Part 2.

9.6. Data Monitoring Committee or Other Review Board

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

ΔHR	Change from baseline in heart rate
ΔPR	Change from baseline in PR interval
ΔQRS	Change from baseline in QRS interval
ΔQTcF	Change from baseline in QT interval corrected for heart rate using Fridericia's formula
ΔΔHR	Placebo-corrected change from baseline in heart rate
ΔΔPR	Placebo-corrected change from baseline in PR interval
ΔΔQRS	Placebo-corrected change from baseline in QRS interval
ΔΔQTcF	Placebo-corrected change from baseline in QT interval corrected for heart rate using Fridericia's formula
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
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
BID	Twice daily
bpm	Beats per minute
CI	Confidence interval
CIB	Clinical Investigator's Brochure
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
C-QTc	Concentration-corrected QT interval
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
$C\tau$	Plasma concentration at the end of the dosing interval
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

FTIH	First-time-in-human
Gag	Group-specific antigen
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
LOAEL	Lowest observed adverse effect level
LS	Least squares
MAD	Multiple-ascending dose
mg	Milligram
MI	Maturation inhibitor
mL	Milliliter
ms	Millisecond
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using the Fridericia formula
QTL	Quality tolerance limit
SAD	Single-ascending dose
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SoA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions

Tmax	Time of maximum observed concentration
TQT	Thorough QT
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
VH	ViiV Healthcare
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
DAIDS
Phoenix WinNonlin
Portia

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 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 3 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 Magnesium	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, urobilinogen, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood, leukocyte esterase, or protein is abnormal)		

Laboratory Assessments	**Parameters**
Other Screening Tests	• Serology: HIV-1 and -2 antigen/antibody immunoassay, hepatitis B surface antigen, hepatitis C antibody • Alcohol, cotinine, and drug screen (to include at minimum amphetamines, barbiturates, cocaine, unprescribed opiates, cannabinoids, benzodiazepines, MDMA, methamphetamines, phencyclidine, oxycodone, methadone, or tricyclic antidepressants) • 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 (WOCBP)

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 enrolment.

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 (WOCBP) 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

- 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 in the study 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 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 SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 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 centere.

- 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.

VH/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.
- VH/GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with VH/GSK Policy.
- VH/GSK intends 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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 participant 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 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 colspan="2">Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td colspan="2">• 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 transaminase [AST], 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, AST, alkaline 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</td><td>• 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 microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.
• Serum acetaminophen adduct high</td></tr>
</table>

Liver Chemistry Stopping Criteria	
	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 <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital 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 <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.6.2. Definition of SAE

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

An 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 PPD and assign it to 1 of the following categories:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

An event is defined as "serious" when it meets at least 1 of the pre-defined 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 IRBs/IECs and National Competent Authorities, as necessary.

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

10.7.1. Changes to Study Visits and Study Procedures

- There may be cases where the current principal investigator of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.

- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

10.7.2. 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 enrollment 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 AEs (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 CRF will be included in the CRF 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.

11. REFERENCES

Bristol-Myers Squibb Company Document Control Number 930109388. A randomized, double-blind, double-dummy, positive-controlled, crossover study to determine electrocardiographic effects of BMS-955176 in healthy subjects. Report Date: January 13, 2017.

Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc. 1979;74(368):829-836.

Darpo B, Benson C, Dota C, et al. Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase. Clin Pharmacol Ther. 2015;97(4):326-335.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005 [cited 25 Jan 2020] [20 screens]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry, Investigators, and Institutional Review Boards. FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency. April 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency.

European Medicines Agency (EMA). Science Medicines Health, Committee for Human Medicinal Products. Points to Consider on Implications of Coronavirus (COVID-19) on methodological Aspects of Ongoing Clinical Trials. March 2020a. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en.pdf.

European Medicines Agency (EMA). Science Medicines Health, Heads of Medicines Agencies. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. April 2020b. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

Ferber G, Zhou M, Darpo B. Detection of QTc Effects in Small Studies--Implications for Replacing the Thorough QT Study. Ann Noninvasive Electrocardiol. 2015;20(4):368-377.

Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. [published correction appears in J Pharmacokinet Pharmacodyn. 2018;45(3):399]. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397.

GlaxoSmithKline Document Number 2018N379610_01. GSK3640254 Investigator's Brochure, Version 02. Effective Date: 24 Oct 2019.

GlaxoSmithKline Document Number 2020N430256_00. A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3640254 in Healthy Participants,. 09 Sep 2018.

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

Huang DP, Chen J, Dang Q, et al. Assay sensitivity in "hybrid thorough QT/QTc (TQT)" study. J Biopharm Stat. 2019;29(2):378-384.

Hurvich CM, Simonoff JS,Tsai CL. Smoothing parameter selection in nonparametric regression using an improved Akaike Information Criterion. J R Stat Soc Series B Stat Methodol. 1998;60(2):271-293.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen - protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37(8):1779-1784.

Malagelada JR and Malagelada C. Nausea and Vomitting. Chapter 15. Sleisenger and Fordtran's Gastrointestinal and Liver Disease 10th edition. 2016. Elsevier.

Millham FH Acute Abdominal Pain. Chapter 11. Sleisenger and Fordtran's Gastrointestinal and Liver Disease 10th edition. 2016. Elsevier.

Morales-Ramirez J, Bogner JR, Molina JM, et al. Safety, efficacy, and dose response of the maturation inhibitor GSK3532795 (formerly known as BMS-955176) plus tenofovir/emtricitabine once daily in treatment-naive HIV-1-infected adults: Week 24 primary analysis from a randomized Phase IIb trial. PLoS ONE. 2018; 13(10): e0205368.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-1043.

Rome Foundation. Rome IV Diagnostic Criteria for Functional Gastrointestinal Disorders. 2019. Available from: https://romeonline.org/?product=rome-iv-diagnostic-algorithms-for-common-gi-symptoms-second-edition. Accessed 18 Feb 2020.

Schiller LR and Sellin J. Diarrhea. Chapter 16. Sleisenger and Fordtran's Gastrointestinal and Liver Disease 10th edition. 2016. Elsevier.

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

Tornøe CW, Garnett CE, Wang Y, Florian J, Li M, Gobburu JV. Creation of a knowledge management system for QT analyses. J Clin Pharmacol. 2011;51(7):1035-1042.

Yarze JC and Friedman LS Chronic Abdominal Pain. Chapter 12. Sleisenger and Fordtran's Gastrointestinal and Liver Disease 10th edition. 2016. Elsevier.