TITLE PAGE

Protocol Title: Open-Label, Single-Sequence Study to Evaluate the Effects of Darunavir/Ritonavir and/or Etravirine on the Pharmacokinetics of GSK3640254 and the Effects of GSK3640254 on the Pharmacokinetics of Darunavir/Ritonavir and/or Etravirine in Heathy Adults

Protocol Number: 213054

Compound Number or Name: GSK3640254

Brief Title: Evaluation of the Effects of Darunavir/Ritonavir and/or Etravirine on the Pharmacokinetics of GSK3640254 and the Effect of GSK3640254 on the Pharmacokinetics of Darunavir/Ritonavir and/or Etravirine in Heathy Adults

Study Phase: Phase 1

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.

Regulatory Agency Identifying Number(s): IND: 139,838

Approval Date: 29-SEP-2020

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Open-Label, Single-Sequence Study to Evaluate the Effects of Darunavir/Ritonavir and/or Etravirine on the Pharmacokinetics of GSK3640254 and the Effects of GSK3640254 on the Pharmacokinetics of Darunavir/Ritonavir and/or Etravirine in Heathy Adults

Brief Title: Evaluation of the Effects of Darunavir (DRV)/Ritonavir (RTV) and/or Etravirine (ETR) on the Pharmacokinetics (PK) of GSK3640254 and the Effect of GSK3640254 on the PK of DRV/RTV and/or ETR in Heathy Adults

Rationale: The current study is being conducted to investigate the effects of DRV/RTV 600/100 mg and/or ETR 200 mg on the PK of GSK3640254 200 mg and the effects of GSK3640254 on the PK of DRV/RTV 600/100 mg and/or ETR 200 mg. This study will aid in understanding these interactions and resulting changes in exposure (if any) when given in combination with GSK3640254.

Objectives and Endpoints:

Objectives		Endpoints
Primary		
Cohort 1	• To assess the effect of co-administration of DRV/RTV 600/100 mg BID with GSK3640254 200 mg QD on the PK of GSK3640254 in healthy participants • To assess the effect of co-administration of DRV/RTV 600/100 mg BID with GSK3640254 200 mg QD on the PK of DRV/RTV in healthy participants.	• AUC(0-tau), and Cmax for GSK3640254 • AUC(0-tau), and Cmax for DRV/RTV
Cohort 2	• To assess the effect of co-administration of ETR 200 mg BID with GSK3640254 200 mg QD on the PK of GSK3640254 in healthy participants. • To assess the effect of co-administration of ETR 200 mg BID with GSK3640254 200 mg QD on the PK of ETR in healthy participants.	• AUC(0-tau), and Cmax for GSK3640254 • AUC(0-tau), and Cmax for ETR
Cohort 3	• To assess the effect of co-administration of ETR 200 mg BID and DRV/RTV 600/100 mg BID with GSK3640254 200 mg QD on the PK of GSK3640254 in healthy participants.	• AUC(0-tau), and Cmax for GSK3640254

Objectives		Endpoints
Secondary		
Cohort 1	• To assess the effect of co-administration of GSK3640254 200 mg QD with DRV/RTV 600/100 mg BID on the secondary PK parameters of DRV and RTV in healthy participants.	• Ctau, and Tmax for DRV, RTV, and GSK3640254
Cohort 2	• To assess the effect of co-administration of GSK3640254 200 mg QD with ETR 200 mg BID on the secondary PK parameters of ETR in healthy participants.	• Ctau, and Tmax for ETR, and GSK3640254
Cohort 1, 2 & 3	• To assess the safety and tolerability of GSK3640254 administered alone and in combination with DRV/RTV and/or ETR.	• Safety and tolerability endpoints include incidence of AEs, SAEs, AEs leading to discontinuation, deaths, marked laboratory abnormalities, and abnormalities in vital signs and 12-lead ECGs.

AE = adverse event; AUC(0-tau) = area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state; BID = twice daily; DRV = darunavir; Cmax = maximum observed concentration, Ctau = plasma concentration at the end of the dosing interval; ECG = electrocardiogram; ETR = etravirine; PK = pharmacokinetics; QD = once daily; RTV = ritonavir; SAE = serious adverse event; Tmax = time of maximum observed concentration.

Overall Design: This is an open-label, single-sequence, multiple-dose, 3 cohort study to investigate the effects of DRV/RTV 600 mg/100 mg and/or ETR 200 mg on the PK of GSK3640254 200 mg and the effects of GSK3640254 200 mg on the PK of DRV/RTV 600/100 mg and/or ETR 200 mg.

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

All doses, of all study interventions will be administered under fed conditions. The participants will fast overnight for at least 8 hours prior to breakfast and before the AM dose and for at least 2 hours prior to dinner and before the PM dose. A moderate fat meal (defined as approximately 600 calories, 30% from fat) will be consumed 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

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

Participants will be confined to the study site from Day -1 until study discharge on Day 35 for Cohort 1, Day 36 for Cohort 2, and Day 26 for Cohort 3. The duration of the study, including screening, is approximately 63 days for Cohort 1, 64 days for Cohort 2, and 54 days for Cohort 3.

Brief Summary: Evaluation of the Effects of DRV/RTV and/or ETR on the PK of GSK3640254 and the Effect of GSK3640254 on the PK of DRV/RTV and/or ETR in Heathy Adults. Study details include:

- Study Duration: 35 days for Cohort 1, 36 days for Cohort 2, and 26 days for Cohort 3
- Treatment Duration: 27 days for Cohort 1 and 2 and 21 days for Cohort 3

Number of Participants: Per cohort, approximately 16 participants will be treated to ensure that 14 evaluable participants complete the study.

Intervention Groups and Duration:

Cohort 1:

- Period 1: GSK3640254 200 mg tablets once daily (QD) (Treatment A) on Days 1 through 7.
- Period 2: DRV/RTV 600/100 mg tablets twice daily (BID) (Treatment B) on Days 12 through 21.
- Period 3: GSK3640254 200 mg tablets QD (Treatment A) and DRV/RTV 600/100 mg tablets BID (Treatment B) on Days 22 through 31.

Cohort 2:

- Period 1: GSK3640254 200 mg tablets QD (Treatment A) on Days 1 through 7.
- Period 2: ETR 200 mg tablets BID (Treatment C) on Days 12 through 21.
- Period 3: GSK3640254 200 mg tablets QD (Treatment A) and ETR 200 mg tablets BID (Treatment C) on Days 22 through 31.

Cohort 3:

- Period 1: GSK3640254 200 mg tablets QD (Treatment A) on Days 1 through 7.
- Period 2: GSK3640254 200 mg tablets QD (Treatment A), DRV/RTV 600/100 mg tablets BID (Treatment B), and ETR 200 mg tablets BID (Treatment C) on Days 8 through 21.

All doses of all study interventions will be administered under fed conditions.

Pharmacokinetic blood samples for the analysis of GSK3640254 will be obtained at the following time points:

- Cohorts 1 and 2:
    - Pre-dose on Days 5, 6, and 7 and up to 24 hours following dosing on Day 7 (Period 1)
    - Pre-dose on Days 29, 30, and 31 and up to 24 hours following dosing on Day 31 (Period 3)
- Cohort 3:
    - Pre-dose on Days 5, 6, and 7 and up to 24 hours following dosing on Day 7 (Period 1)

- Pre-dose and up to 24 hours following dosing on Day 21 (Period 2)

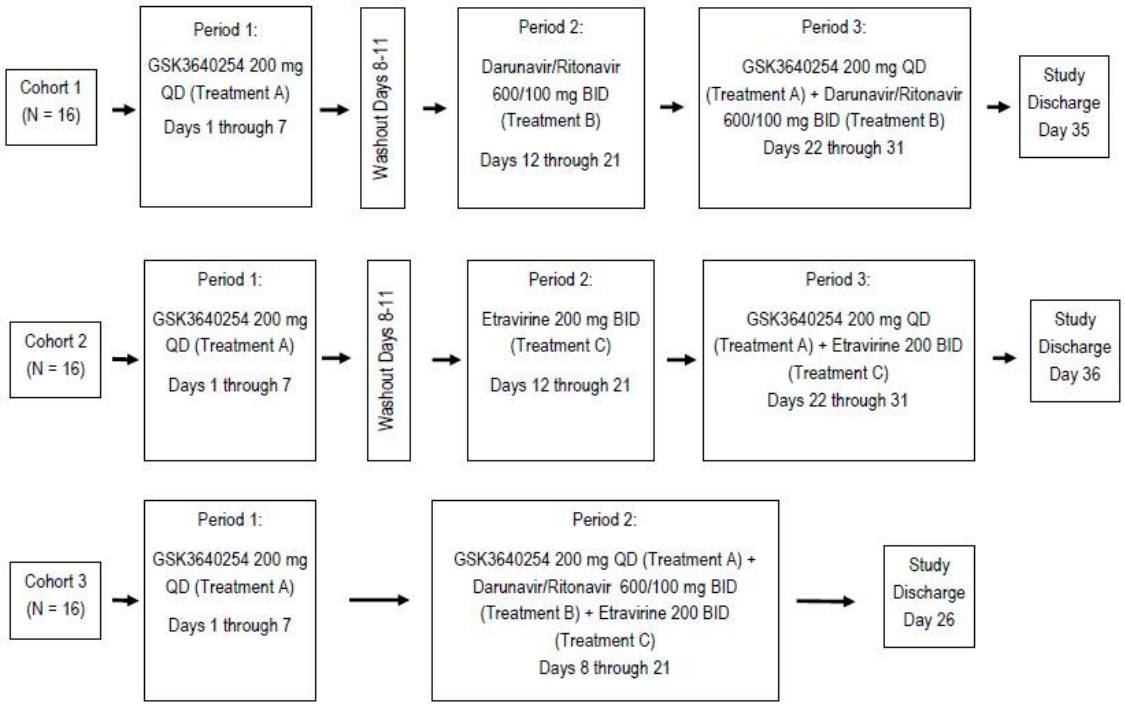
Pharmacokinetic blood samples for the analysis of DRV/RTV and/or ETR will be obtained at the following time points:

- Cohorts 1 and 2:
  - Pre-dose on Days 19, 20, and 21 and up to 12 hours following dosing on Day 21 (Period 2)
  - Pre-dose and up to 12 hours following dosing on Day 31 (Period 3)
- Cohort 3:
  - Pre-dose on Days 19, 20, and 21 and up to 12 hours following dosing on Day 21 (Period 3)

The duration of the study, including screening, is approximately 63 days for Cohort 1, 64 days for Cohort 2, and 54 days for Cohort 3.

Data Monitoring/Other Committee: No

1.2. Schema



BID = twice daily; N = number of participants; QD = once daily.

1.3. Schedule of Activities (SoA)

- Screening procedures may be completed over more than 1 visit, but must all be completed within 28 days prior to the first dose of study intervention.
- The following demographic parameters will be captured: year of birth, sex, race, and ethnicity.

- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria.

Screening Visit

Procedure	Screening (up to 28 days before Day 1)
Outpatient visit	X
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight [1]	X
Laboratory assessments (hematology, clinical chemistry, urinalysis)	X
12-lead electrocardiogram	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Columbia-Suicide Severity Rating Scale	X
Serum pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
Drug, alcohol, and cotinine screen	X
Human immunodeficiency virus, Hepatitis B and C screening	X
Molecular test for SARS-CoV-2[2]	X

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

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment B (Days 12-21)		Period 3 Treatment A +Treatment B (Days 22-31)									Notes
	Day -2	D -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-34	Day 35	
Admit to clinic	X																		
Discharge from clinic																		X	
Brief physical examination	X				X		X		X				X					X	Includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
Vital sign measurements	X	X	X	D2	X		X	D12, D13, D17		X	X		X					X	Blood pressure and pulse measured in triplicate at pre-dose on Days 1, 12, and 22. Single blood pressure and pulse will be measured on other study days.
Temperature Check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment B (Days 12-21)		Period 3 Treatment A +Treatment B (Days 22-31)									Notes
	Day -2	D -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-34	Day 35	
12-lead ECG	X	X	X		X		X	D12	X	X			X					X	ECGs on Days 1, 12, and 22, will be taken pre-dose, and at 2 and 4 and 6 hours post-dose. Pre-dose ECGs on Days 1, 12, and 22 will be taken in triplicate. The post-dose ECGs are single ECGs.
Drug, alcohol, and cotinine screen	X																		See Appendix 2 for tests.
Laboratory assessments (hematology, clinical chemistry, urinalysis)	X				X		X		X				X					X	See Appendix 2 for tests.

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment B (Days 12-21)		Period 3 Treatment A +Treatment B (Days 22-31)									Notes
	Day -2	D -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-34	Day 35	
Molecular test for SARS-CoV-2	X[1]			D6				D13, D20						D27				X	Test to be obtained every 7 days from Check-in (regardless of period or washout) while in-house. [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.
Pregnancy test	X																	X	Urine pregnancy test to confirm status.
Columbia-Suicide Severity Rating Scale	X				X					X					X				See Section 8.2.6 for details.
Study intervention: DRV/RTV (BID)								X	X	X	X	X	X	X	X				See Section 6.1 for study intervention details.

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment B (Days 12-21)		Period 3 Treatment A +Treatment B (Days 22-31)									Notes
	Day -2	D -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-34	Day 35	
Study intervention: GSK3640254 200 mg (QD)			X	X	X					X	X	X`	X	X	X				See Section 6.1 for study intervention details.
DRV/RTV PK sampling								D19, D20	X						X				Pre-dose Days 19, 20 and 21. Post Day 21 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose. Pre-dose Day 31. Post Day 31 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours.
GSK3640254 PK sampling				D5, D6	X	D8								D29, D30	X	X			Pre-dose Days 5, 6, and 7. Post Day 7 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours. Pre-dose Days 29, 30, and 31. Post Day 31 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours.
AE review	←==========→																		
SAE review	←==========→																		
Concomitant medication review	←==========→																		

Abbreviations: AE = adverse event; BID = twice daily; D = day; DRV = darunavir; ECG = electrocardiogram; PK = pharmacokinetic; QD = once daily; RTV = ritonavir; SAE = serious adverse event.

Time and Events Table - Cohort 2

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment C (Days 12-21)		Period 3 Treatment A +Treatment C (Days 22-31)									Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-35	Day 36	
Admit to clinic	X																		
Discharge from clinic																		X	
Brief physical examination	X				X		X		X				X					X	Includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
Vital sign measurements	X	X	X	D2	X		X	D12, D13, D17		X	X		X					X	Blood pressure and pulse measured in triplicate at pre-dose on Days 1, 12, and 22. Single blood pressure and pulse will be measured on other study days.
Temperature Check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment C (Days 12-21)		Period 3 Treatment A +Treatment C (Days 22-31)									Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-35	Day 36	
12-lead ECG	X	X	X		X		X	D12	X	X			X					X	ECGs on Days 1, 12, and 22, will be taken pre--dose, and at 2, 4, and 6 hours post-dose. Pre-dose ECGs on Days 1, 12, and 22 will be taken in triplicate. The post-dose ECGs are single ECGs.
Drug, alcohol, and cotinine screen	X																		See Appendix 2 for tests.
Laboratory assessments (hematology, clinical chemistry, urinalysis)	X				X		X		X				X					X	See Appendix 2 for tests.

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment C (Days 12-21)		Period 3 Treatment A +Treatment C (Days 22-31)									Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-35	Day 36	
Molecular test for SARS-CoV-2	X[1]			D6				D13, D20						D27				X	Test to be obtained every 7 days from Check-in (regardless of period or washout) while in-house. [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.
Pregnancy test	X																	X	Urine pregnancy test to confirm status.
Columbia-Suicide Severity Rating Scale	X				X					X					X				See Section 8.2.6 for details.
Study intervention: ETR (BID)								X	X	X	X	X	X	X	X				See Section 6.1 for study intervention details.

Procedure	Check-In	Baseline	Period 1 Treatment A (Days 1-7) Washout (Days 8-11)					Period 2 Treatment C (Days 12-21)		Period 3 Treatment A +Treatment C (Days 22-31)									Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8-10	Day 11	Days 12-20	Day 21	Day 22	Day 23	Days 24-25	Day 26	Days 27-30	Day 31	Day 32	Days 33-35	Day 36	
Study intervention: GSK3640254 200 mg (QD)			X	X	X					X	X	X`	X	X	X				See Section 6.1 for study intervention details.
ETR PK sampling								D19, D20	X						X				Pre-dose Days 19, 20 and 21. Post Day 21 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose. Pre-dose Day 31. Post Day 31 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours.
GSK3640254 PK sampling				D5, D6	X	D8								D29, D30	X	X			Pre-dose Days 5, 6, and 7. Post Day 7 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours. Pre-dose Days 29, 30, and 31. Post Day 31 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours.
AE review	←==========→																		
SAE review	←==========→																		
Concomitant medication review	←==========→																		

Abbreviations: AE = adverse event; BID = twice daily; D = day; ECG = electrocardiogram; ETR = etravirine; PK = pharmacokinetic; QD = once daily; SAE = serious adverse event.

Time and Events Table - Cohort 3

Procedure	Check-in	Baseline	Period 1 Treatment A (Days 1-7)			Period 2 Treatment A + Treatment B + Treatment C (Days 8-21)												Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8	Day 9	Days 10-12	Day 13	Day 14	Days 15-16	Day 17	Days 18-20	Day 21	Day 22	Days 23-25	Day 26	
Admit to clinic	X																	
Discharge from clinic																	X	
Brief physical examination	X				X					X							X	Includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
Vital sign measurements	X	X	X	D2	X	X				X		X					X	Blood pressure and pulse measured in triplicate at pre-dose on Days 1 and 8. Single blood pressure and pulse will be measured on other study days.
Temperature Check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X	X			X	X										X	ECGs on Day 1 will be taken pre-dose, and at 2, 4, and 6 hours post-dose. ECGs on Days 8 and 9 will be taken at 2, 4 and 6 hours post dose. Pre-dose ECGs on Day 1 will be taken in triplicate. The post-dose ECGs are single ECGs.
Drug, alcohol, and cotinine screen	X																	See Appendix 2 for tests.

Procedure	Check-in	Baseline	Period 1 Treatment A (Days 1-7)			Period 2 Treatment A + Treatment B + Treatment C (Days 8-21)												Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8	Day 9	Days 10-12	Day 13	Day 14	Days 15-16	Day 17	Days 18-20	Day 21	Day 22	Days 23-25	Day 26	
Laboratory assessments (hematology, clinical chemistry, urinalysis)	X				X					X							X	See Appendix 2 for tests.
Molecular Test for SARS-CoV-2	X[1]			D6					X				D20				X	Test to be obtained every 7 days from Check-in (regardless of period or washout) while in-house. [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.
Pregnancy test	X																X	Urine pregnancy test to confirm status.
Columbia-Suicide Severity Rating Scale	X				X	X			X					X				See Section 8.2.6 for details.

Procedure	Check-in	Baseline	Period 1 Treatment A (Days 1-7)			Period 2 Treatment A + Treatment B + Treatment C (Days 8-21)												Notes
	Day -2	Day -1	Day 1	Days 2-6	Day 7	Day 8	Day 9	Days 10-12	Day 13	Day 14	Days 15-16	Day 17	Days 18-20	Day 21	Day 22	Days 23-25	Day 26	
Study intervention: DRV/RTV and ETR (BID)						X	X	X	X	X	X	X	X	X				See Section 6.1 for study intervention details.
Study intervention: GSK3640254 200 mg (QD)			X	X	X	X	X	X	X	X	X`	X	X	X				See Section 6.1 for study intervention details.
DRV/RTV and ETR PK sampling													D19, D20	X				Pre-dose Days 19, 20, and 21. Post Day 21 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours.
GSK3640254 PK sampling				D5, D6	X	X								X	X			Pre-dose Days 5, 6, and 7. Post Day 7 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours. Pre-dose Day 21. Post Day 21 dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours.
AE review	←==========																==========→	
SAE review	←==========																==========→	
Concomitant medication review	←==========																==========→	

AE = adverse event; BID = twice daily; D = day; DRV = darunavir; ECG = electrocardiogram; ETR = etravirine; PK = pharmacokinetic; QD = once daily; RTV = ritonavir; SAE = serious adverse event.

- Participants will fast overnight for at least 8 hours prior to breakfast and before the AM dose and for at least 2 hours prior to dinner and before the PM dose. Participants will receive the moderate fat meal 30 minutes prior to dosing. Participants will eat this meal

in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Refer to Section 5.3.1 for meal timings.

- Serial PK blood samples will be collected before (at 0 hour) and after the AM study drug administration at the time points listed. For the study interventions that are administered twice daily (BID) (DRV/RTV and ETR), the 12-hour sample will be collected before the PM dose.
- Day 35 for Cohort 1, Day 36 for Cohort 2, and Day 26 for Cohort 3 is study discharge. Evaluations scheduled for study discharge will also be performed for participants who discontinue prior to completing.
- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing 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 health authority and the ethics committee before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is a randomized, open-label, single-sequence, multi-dose study to investigate the effects of GSK3640254 200 mg on the pharmacokinetics (PK) of darunavir (DRV)/ritonavir (RTV) 600/100 mg and/or etravirine (ETR) 200 mg and the effects of DRV/RTV 600/100 mg and/or ETR 200 mg on the PK of GSK3640254. This study will aid in understanding these interactions and resulting changes in exposure (if any) when given in combination with GSK3640254.

2.2. Background

GSK3640254 is a 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 relationship and longer-term efficacy through Phase 2a and 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 205891. 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 and 2 diarrhea in 38 to 61% of participants and abdominal pain in 8 to 22% of participants, respectively) and a higher rate of nucleoside reverse transcriptase inhibitor resistance (6.5%) with clinically significant changes in GSK3532795 susceptibility which was observed across all 3 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 I thorough QT study AI468044/206220 [Bristol-Myers Squibb Document Number 930109388] at supra-therapeutic doses: 1 healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The 2 participants received GSK3532795 240 mg

twice daily and 240 mg once daily (QD) with food, respectively. These events were assessed as related to study drug but were not observed in any other clinical trial with GSK3532795. The most frequent neuropsychiatric adverse events (AEs) in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia and abnormal dreams).

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

2.2.2. Summary of GSK3640254 Clinical Pharmacokinetics

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

- Following multiple-dose administration over 50 to 320 mg dose range for 14 days with a moderate fat meal in the single ascending dose (SAD)/multiple ascending dose (MAD) first time in human (FTIH) Study 207187:
    - Median time of maximum observed concentration (Tmax) ranged between 3.8 to 4.3 hours.
    - The mean half-life ranged from approximately 22 to 29 hours.
    - There was a slightly less than dose-proportional increase in maximum observed concentration (Cmax) and area under the plasma concentration-time curve (AUC) from time zero to the end of the dosing interval at steady state (AUC[0-tau]) 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-tau) compared to those on Day 1, which is an agreement with half-life estimates.
    - PK variability (between-subject variability) was modest, 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].

2.2.3. Summary of GSK3640254 Metabolism

GSK3640254 had low oxidative intrinsic clearance in mouse, rat, dog, monkey, and human liver microsomes and hepatocytes. Metabolic pathways observed *in vitro* across

species mainly included mono-oxidation, N-dealkylation, and direct glucuronidation, with no unique metabolites generated in human liver microsomes or hepatocytes and no evidence of metabolic activation. An acyl glucuronide metabolite was formed via direct glucuronidation of GSK3640254 and the acyl glucuronide of GSK3640254 was found to be stable under conditions of physiological pH and temperature. With recombinant cytochrome P450 (CYP) enzymes, GSK3640254 was mainly metabolized by CYP3A4/3A5, CYP2C9, CYP1A2 and CYP2C8. GSK3640254 was stable in recombinant uridine diphosphate glucuronosyltransferase 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. None of the circulating metabolites in human plasma were quantifiable by nuclear magnetic resonance analysis. Additional information regarding GSK3640254 metabolism can be found in the CIB [GSK Document Number 2018N379610_01].

2.2.4. Preclinical Summary with GSK3640254

Pharmacokinetics and product metabolism in animals

Following intravenous administration, GSK3640254 exhibited low systemic clearance, high volume distribution, and elimination half-life 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 human, there is a potential risk for GSK3640254 to act as a perpetrator of drug-drug interactions (DDIs) of substrates of OATP1B3 and MRP2. GSK3640254 was an inhibitor of UGT1A1 and clinical DDIs via this mechanism could be possible.

Toxicology

The primary target organ of toxicity in non-clinical studies with GSK3640254 was stomach, with microscopic changes affecting parietal and chief cells in mice, rats and dogs. Following four weeks of dosing in rats, the no observed adverse effect level (NOAEL) for microscopic findings in the stomach was 10 mg/kg/day (AUC = 22.4 ug.hr/mL). In the 4-week studies in rats and dogs, microscopic findings in the stomach

minimal and reversible at the lowest observed adverse effect levels (LOAEL) of 30 and 1 mg/kg/day (AUC = 61.1 and 73.3 ug.hr/mL, respectively), similar to the highest anticipated exposure in this study (60 ug.hr/mL).

With correction for protein binding, compared to the IC_{50} for the hERG/IKr potassium channel, there is an 8.8-fold margin above the highest anticipated plasma concentration (C_{max}=4.4 ug/mL) 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 approximately 2-fold higher than the highest anticipated C_{max} in this study. In addition, there were no effects on electrocardiogram (ECG) parameters in dogs given up to 25 mg/kg/day for 4 weeks at 9.75-fold above the highest anticipated C_{max} in this study.

2.2.5. Summary of GSK3640254 Safety

A summary of safety data from the clinical studies 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 to 4 AEs included: 1) headache (2 participants both Grade 2; 1 participant in Studies 207187 and 208132, each), 2) nausea (2 participants both Grade 2; 1 participant in Studies 208134 and 208132, each), and abdominal pain (1 participant with Grade 2 AE in Study 208132).
- Clinically notable AEs of elevated transaminases occurred in Studies 207187 (SAD/MAD, n = 1 healthy participant) and 208135 (DDI with oral contraceptive Portia [0.03mg ethinyl estradiol/0.15mg levonorgestrel], n = 8 healthy participant). Subsequent analysis in Study 208135 showed no PK/pharmacodynamic relationship with either GSK3640254 or Portia (0.03mg ethinyl estradiol/0.15mg levonorgestrel) 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, or concomitant medication administration were: headache (11.9%), contact dermatitis and related events (7.8%), diarrhea (5.5%), and abdominal pain (4.1%).

- Across studies, low grade GI intolerability has been observed: the majority were mild. Both Studies 207187 (MAD) and 208312 (proof of concept) are relevant to this study given dosing of 7 to 14 days; most AEs in 207187 were unrelated and most AEs in 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 msec or an increase from baseline >60 msec.

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

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

2.2.5.1. 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 (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; note, the dose used in the current study will be 200 mg QD).

2.2.6. Drug Interaction Potential with Darunavir/Ritonavir and Etravirine

This study is being conducted to investigate any potential DDIs when GSK3640254 is co-administered with DRV/RTV and ETR. Darunavir/RTV and ETR are commonly used in HIV-infected treatment-experienced (HTE) patients. GSK3640254 is primarily metabolized by CYP3A4/3A5, CYP2C9, CYP1A2, and CYP2C8. Co-administration of GSK3640254 with DRV/RTV may increase GSK3640254 exposure due to inhibition of CYP3A4 by DRV/RTV. Etravirine is a substrate and moderate inducer of CYP3A4 and a weak inhibitor of CYP2C9, CYP2C19, and P-glycoprotein (P-gp). Thus, co-administration of GSK3640254 with ETR may decrease or increase GSK3640254

exposure. Co-administration of GSK3640254 with both DRV/RTV and ETR may result in no net effect.

The mean systemic exposure (AUC) of ETR was reduced when ETR was co-administered with DRV/RTV. Because all participants in the Phase 3 studies received DRV/RTV as part of the background regimen and ETR exposures from these studies were determined to be safe and effective, ETR and DRV/RTV can be co-administered without dose adjustments [Intelence Product Information, 2019].

Ritonavir (Norvir)

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the Gag-pol polyprotein precursor, which leads to production of noninfectious immature HIV particles. The PK behavior of RTV has been studied in healthy participants and HIV-infected patients. After a 600-mg dose of oral solution, peak concentrations of RTV were achieved approximately 2 and 4 hours after dosing under fasting and non-fasting conditions, respectively. In vitro studies utilizing human liver microsomes have demonstrated that CYP3A is the major isoform involved in RTV metabolism, although CYP2D6 also contributes. Ritonavir inhibits CYP3A in vitro and in vivo. Agents that are extensively metabolized by CYP3A and have high first-pass metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when co-administered with RTV. Ritonavir also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with RTV could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A as well as other enzymes, including glucuronosyl transferase, CYP1A2, and possibly CYP2C9 and CYP2C19.

Ritonavir is rarely used as monotherapy at the original therapeutic dose of 600 mg administered BID because of the high incidence of a variety of side effects. The fact that RTV is a potent inhibitor of CYP-based metabolism has been employed to increase the exposure of other co-administered HIV protease inhibitors, which are better tolerated [Aarnoutse, 2004; Piliero, 2001]. Ritonavir achieves its metabolic inhibition at doses, which are much lower than therapeutic; for example, 100 mg QD when combined with atazanavir will boost the Cmax and AUC of atazanavir [Norvir Product Information, 2019]. The most frequent AEs reported in participants receiving RTV as monotherapy or in combination with nucleoside analogues include asthenia, nausea, vomiting, abdominal pain, diarrhea, anorexia, taste perversion, circumoral paresthesia, peripheral neuropathy, dizziness, and insomnia. Laboratory abnormalities reported with the use of RTV include elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, nonfasting triglyceride, cholesterol, creatine phosphokinase, and uric acid. The frequency of AEs following administration of low-dose RTV is not well known, as it would not be administered alone, in such low doses. However, it is expected that the incidence of AEs would be reduced at low doses.

Darunavir (Prezista)

Darunavir is an inhibitor of HIV-1 protease. Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of DRV. When a single dose of DRV 600 mg was given orally in combination with 100 mg RTV BID, there was an approximate 14-fold increase in the systemic exposure of DRV. Therefore, DRV is used in combination with 100 mg of RTV to achieve sufficient exposures of DRV.

The PK behavior of DRV co-administered with low dose RTV (100 mg) has been studied in healthy participants and HIV-infected patients (Prezista Product Information, 2019). Following 600 mg DRV co-administered with 100 mg RTV BID orally, a Tmax of approximately 2.5 to 4 hours was established. The terminal elimination half-life of DRV was approximately 15 hours when co-administered with RTV. The absolute oral bioavailability of a single 600-mg dose of DRV alone and after co-administration with 100 mg RTV BID was 37% and 82%, respectively. When DRV was administered with food, the Cmax and AUC of DRV, co-administered with RTV, are approximately 40% higher relative to the fasting state. Therefore, DRV, co-administered with RTV, should always be taken with food. Within the range of meals studied, DRV exposure is similar. In vivo data suggest that DRV/RTV is an inhibitor of the P-gp transporters. Additionally, DRV is extensively metabolized by CYP enzymes, primarily by CYP3A.

In clinical studies of HIV treatment-naïve participants receiving DRV 800 mg and RTV 100 mg QD, the majority of AEs reported were mild in severity. The most common AEs were diarrhea, headache, abdominal pain, and rash. Less common AEs included acute pancreatitis, dyspepsia, flatulence, asthenia, acute hepatitis, hypersensitivity, diabetes mellitus, myalgia, abnormal dreams, angioedema, pruritus, Stevens-Johnson syndrome, and urticaria.

Etravirine (Intelence™)

Etravirine in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in antiretroviral-treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor and other antiretroviral agents. The PK behavior of ETR has been studied in healthy participants and treatment-experienced HIV-infected patients. Following oral administration, ETR was absorbed with a Tmax of approximately 2.5 to 4 hours. The absolute oral bioavailability is unknown [Intelence Product Information, 2019]. The systemic exposure (AUC) to ETR was decreased by approximately 50% when administered under fasting conditions compared with when administered after a meal. Within the range of meals studied, the systemic exposures to ETR were similar.

In vitro experiments with human liver microsomes indicate that ETR primarily undergoes metabolism by CYP3A, CYP2C9, and CYP2C19 enzymes. Etravirine is an inducer of CYP3A and inhibitor of CYP2C9, CYP2C19, and P-gp. Therefore, co-administration of drugs that are inhibitors, inducers, or substrates of CYP3A, CYP2C9, and CP2C19 or are transported by P-gp with ETR may alter the therapeutic effect or adverse reaction profile of ETR and/or the co-administered drug(s). The most common AEs reported after administration of ETR include rash, Stevens-Johnson syndrome, hypersensitivity

reaction, and erythema multiforme. Some of the AEs reported in HIV-infected participants are not expected in healthy participants. Darunavir co-administered with low dose RTV and ETR 200 mg twice daily can be used without dose adjustments.

Given the complexity of the drug-drug interaction mechanism, an estimation of the extent of the expected interaction is difficult. However, data from a similar DDI study conducted with the structurally-similar prior MI GSK3532795, showed a maximum increase in GSK3532795 Cmax and AUC(0-τ) of approximately two-fold, following coadministration with DRV/RTV (600/100 mg BID) and ETR (200 mg BID). A similar fold increase in exposure for GSK3640254 would result in a Cmax and AUC at steady state of approximately 4.4 ug/mL and 60 ug.hr/mL, respectively.

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 diarrhea) and gastric toxicity (effects on parietal cell and chief cells), prolongation of the QTc, neuropsychiatric safety, and rash.

First, GI intolerability will be assessed using clinical monitoring as outlined in Section 8.2.7.

Second, prolongation of the QTc interval is a risk. One preclinical trial 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 is summarized above (Phase 2b study). Importantly, in GSK3640254 clinical studies to date, there have been no abnormal clinically significant arrhythmias, and no participants met the trial based QTc stopping criteria for QTcF prolongations: values >500 ms or increases >60 ms from baseline. This study contains specific cardiac exclusion criteria, has ECG monitoring (at Tmax once GSK3640254 attains steady state concentration), and has QTcF based stopping criteria (See Section 7.1.2).

Third, given the risk of psychiatric risks seen with GSK3532795 (see 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). 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 (See Section 7.1.4 and Section 8.2.6).

Across clinical trials, 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.

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].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Preclinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with complementary deoxyribonucleic acid (DNA) from the ion channels. In a single-dose safety pharmacology study in telemeterized dogs, increases in QT interval (up to 20 ms) occurred primarily in 1 dog given 17 mg/kg. The no observed adverse effect level in the study was 12.5 mg/kg, which produced similar systemic exposures (8.79 µg/mL, 2 × the mean Cmax associated with the highest anticipated exposure (4.4 µg/mL) in the this 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 and cardiac medical history. **On-Treatment:** Participants will have ECG monitoring (at a clinically reasonable frequency) during the course of the study (see SoA, Section 1.3) with QTc stopping criteria (see Section 7.1.2).
GI intolerability and toxicity	Observations indicative of GI intolerability (sporadic vomiting and abnormal feces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells were present in preclinical species. In a 4-week oral toxicity study in rats, at the lowest affected dose of 30 mg/kg/day (AUC=61.1 ug.hr/mL, approximately equal to the highest anticipated exposure in this study), these findings were minimal and reversible. Gastrointestinal intolerability (predominantly abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was	**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 is available to guide investigators should GI AEs emerge (see Section 8.2.7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	evaluated through Phase 2b dosing. (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]). No clinical trends in the system organ class of GI AEs have been seen across Phase 1 to 2a GSK3640254 clinical trials.	
Neurologic/psychiatric safety	Two psychiatric SAEs in previous maturation inhibitor GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) were seen at supratherapeutic doses in healthy participants in the thorough QT (TQT) study. From a neurologic and psychiatric AE summary and PK/pharmacodynamic analysis for GSK3532795 across all studies, Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and Phase 2b studies). No exposure-response relationship was seen for select neurologic and psychiatric AEs (based on TQT and Phase 2b studies). Central nervous system penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. No clinical trends in the system organ class of neurologic or psychiatric AEs have been observed across the Phase 1 to 2a clinical trials.	**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 7.1.5 and Section 8.2.6). 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 behavior, as determined by the investigator (in consultation with psychiatry, as needed), the participant will discontinue from the study and the investigator will arrange for urgent specialist psychiatric evaluation and management. Guidance for the investigator on the management of emergent psychiatric symptoms is available (Section 8.2.6).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Rash	Across clinical trials, 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 trial supplemented by the use of physical exams. Protocol includes individual participant stopping criteria, including: • Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement • Any allergic or hypersensitivity reactions (Section 7.1.3)
Darunavir/Ritonavir		
Drug-induced hepatitis	Drug-induced hepatitis has been reported with DRV/RTV.	**Screening**: Protocol exclusion criteria based on screening liver function tests. **On-Treatment**: Participants will be monitored by clinical laboratory testing for liver function tests (see SoA, Section 1.3) with protocol defined stopping criteria (see Section 7.1.5.
Etravirine		
Skin reactions	Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions including drug rash with eosinophilia and symptoms have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.	**Screening:** A physical examination of the skin will be performed at screening. **On Treatment:** Participants will have brief physical examinations that will include assessment of the skin at specific time points throughout the study (See SoA, Section 1.3). Participants presenting with a Grade 3 or higher rash or a Grade 2 rash with evidence of systemic involvement will be followed until AE resolution per Section 7.1.3. Skin stopping criteria can be found in Section 7.1.3.

2.3.2. Benefit Assessment

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

2.3.3. Overall Benefit: Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the clinical data gathered from Phase 1 and 2a studies, and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 and co-administered multiple doses of the potential interaction drugs are low, evaluable, and manageable.

The drugs with the potential for a drug interaction in this study are commonly used in clinical practice for HIV-1 infected patients and have 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 with the drugs of potential interaction, the safety risk of participation in this study is expected to be low. To minimize risk further, the protocol contains exclusions relevant to the study intervention and prohibits the concurrent intake of potentially interacting drugs or foods that might increase the concentrations of study intervention.

3. OBJECTIVES AND ENDPOINTS

Objectives		Endpoints
Primary		
Cohort 1	• To assess the effect of co-administration of DRV/RTV 600/100 mg BID with GSK3640254 200 mg QD on the PK of GSK3640254 in healthy participants • To assess the effect of co-administration of DRV/RTV 600/100 mg BID with GSK3640254 200 mg QD on the PK of DRV/RTV in healthy participants.	• AUC(0-tau), and Cmax for GSK3640254 • AUC(0-tau), and Cmax for DRV/RTV
Cohort 2	• To assess the effect of co-administration of ETR 200 mg BID with GSK3640254 200 mg QD on the PK of GSK3640254 in healthy participants. • To assess the effect of co-administration of ETR 200 mg BID with GSK3640254 200 mg QD on the PK of ETR in healthy participants.	• AUC(0-tau), and Cmax for GSK3640254 • AUC(0-tau), and Cmax for ETR
Cohort 3	• To assess the effect of co-administration of ETR 200 mg BID and DRV/RTV 600/100 mg	• AUC(0-tau), and Cmax for GSK3640254

Objectives		Endpoints
	BID with GSK3640254 200 mg QD on the PK of GSK3640254 in healthy participants.	
Secondary		
Cohort 1	• To assess the effect of co-administration of GSK3640254 200 mg QD with DRV/RTV 600/100 mg BID on the secondary PK parameters of DRV and RTV in healthy participants.	• Ctau, and Tmax for DRV, RTV, and GSK3640254
Cohort 2	• To assess the effect of co-administration of GSK3640254 200 mg QD with ETR 200 mg BID on the secondary PK parameters of ETR in healthy participants.	• Ctau, and Tmax for ETR, and GSK3640254
Cohort 1, 2 & 3	• To assess the safety and tolerability of GSK3640254 administered alone and in combination with DRV/RTV and ETR.	• Safety and tolerability endpoints include incidence of AEs, SAEs, AEs leading to discontinuation, deaths, marked laboratory abnormalities, and abnormalities in vital signs and 12-lead ECGs.

AE = adverse event; AUC(0-tau) = area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state; BID = twice daily; DRV = darunavir; Cmax = maximum observed concentration, Ctau = plasma concentration at the end of the dosing interval; ECG = electrocardiogram; ETR = etravirine; PK = pharmacokinetics; QD = once daily; RTV = ritonavir; SAE = serious adverse event; Tmax = time of maximum observed concentration.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-sequence, multiple-dose, 3 cohort study to investigate the effects of DRV/RTV 600 mg/100 mg and/or ETR 200 mg on the PK of GSK3640254 200 mg and the effects of GSK3640254 200 mg on the PK of DRV/RTV 600/100 mg and/or ETR 200 mg.

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

Participants will be randomly assigned to a cohort and will receive the following treatments in each cohort:

Cohort 1:

- Period 1: GSK3640254 200 mg tablets QD (Treatment A) on Days 1 to 7.
- Period 2: DRV/RTV 600/100 mg tablets BID (Treatment B) on Days 12 through 21.

- Period 3: GSK3640254 200 mg tablets QD (Treatment A) and DRV/RTV 600/100 mg tablets BID (Treatment B) on Days 22 through 31.

Cohort 2:

- Period 1: GSK3640254 200 mg tablets QD (Treatment A) on Days 1 to 7.
- Period 2: ETR 200 mg tablets BID (Treatment C) on Days 12 through 21.
- Period 3: GSK3640254 200 mg tablets QD (Treatment A) and ETR 200 mg tablets BID (Treatment C) on Days 22 through 31.

Cohort 3:

- Period 1: GSK3640254 200 mg tablets QD (Treatment A) on Days 1 to 7
- Period 2: GSK3640254 200 mg tablets QD (Treatment A), DRV/RTV 600/100 mg tablets BID (Treatment B), and ETR 200 mg tablets BID (Treatment C) on Days 8 through 21

All doses of all study interventions will be administered under fed conditions. The participants will fast overnight for at least 8 hours prior to breakfast and before the AM dose and for at least 2 hours prior to dinner and before the PM dose. A moderate fat meal (defined as approximately 600 calories, 30% from fat) will be consumed 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Pharmacokinetic blood samples for the analysis of GSK3640254 will be obtained at the following time points:

- Cohorts 1 and 2:
    - Pre-dose on Days 5, 6, and 7 and up to 24 hours following dosing on Day 7 (Period 1)
    - Pre-dose on Days 29, 30, and 31 and up to 24 hours following dosing on Day 31 (Period 3)
- Cohort 3:
    - Pre-dose on Days 5, 6, and 7 and up to 24 hours following dosing on Day 7 (Period 1)
    - Pre-dose and up to 24 hours following dosing on Day 21 (Period 2)

Pharmacokinetic blood samples for the analysis of DRV/RTV and/or ETR will be obtained at the following time points:

- Cohorts 1 and 2:
    - Pre-dose on Days 19, 20, and 21 and up to 12 hours following dosing on Day 21 (Period 2)
    - Pre-dose and up to 12 hours following dosing on Day 31 (Period 3)
- Cohort 3:
    - Pre-dose on Days 19, 20, and 21 and up to 12 hours following dosing on Day 21 (Period 3).

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

Study assessments will be performed as indicated in the Schedule of Activities (SoA) (Section 1.3). Participants will be confined to the study site from Day -1 until study discharge on Day 35 for Cohort 1, Day 36 for Cohort 2, and Day 26 for Cohort 3. The duration of the study, including screening, is approximately 63 days for Cohort 1, 64 days for Cohort 2, and 54 days for Cohort 3.

4.2. Scientific Rationale for Study Design

This study is being conducted to investigate any potential DDIs when GSK3640254 is co-administered with DRV/RTV and/or ETR. Darunavir/RTV and ETR are commonly used in treatment experienced (including Heavily Ttreatment Experienced) HIV-1 infected patients.

GSK3640254 is primarily metabolized by CYP3A4/3A5, CYP2C9, CYP1A2, and CYP2C8. The co-administration of DRV/RTV with GSK3640254 may increase GSK3640254 exposure due to inhibition of CYP3A4 by DRV/RTV. The co-administration of ETR with GSK3640254 may decrease GSK3640254 exposure due to induction of CYP3A4 by ETR. Co-administration of GSK3640254 with DRV/RTV and ETR may result in no net effect on any of the PK parameters.

This study is designed in accordance with the US Food and Drug Administration Guidance for Industry, Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications [DHHS, 2017] to assess the PK, safety, and tolerability of GSK3640254 and the drugs of potential interaction when administered alone and in combination. The drugs with potential for a DDI used in this study are DRV/RTV 600/100 mg and ETR 200 mg.

4.3. Justification for Dose

A dose of 200 mg GSK3640254 was selected for this study as it is the maximum projected clinical dose. The apparent terminal phase half-life of GSK3640254 was approximately 22 hours in the MAD portion of Study 207187 [GSK Document Number 2020N430256_00] at the 200-mg dose and predicted time to steady state is approximately 5 days. The 200 mg dose is the top dose to be evaluated in a longitudinal Phase 2b dose range finding study of GSK3640254 (Study 208379).

Dosing of GSK3640254 QD from Days 1 to 7 (Period 1) and Days 22 to 31 (Period 3) in Cohorts 1 and 2 will be sufficient to bring plasma concentrations to steady state. For Cohort 3, there is no subsequent need for a washout of GSK3640254 following Period 1 since the primary remaining evaluation is for the co-administered DRV/RTV and ETR and GSK3640254 at steady state.

Doses of DRV/RTV 600/100 mg BID and ETR 200 mg BID are commonly used for HIV-1 infected patients . Further information on DRV/RTV and ETR is provided in Section 2.2.4.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

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

Sex and Contraceptive/Barrier Requirements

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

b. Female participants:

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

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

   OR

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

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

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

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 4, which includes compliance with the requirements and restrictions listed in the 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., gastroesophageal reflux disease, gastric ulcers, gastritis) or hepatic and/or renal function that could interfere with the absorption, metabolism, and/or excretion of the study intervention or render the participant unable to take oral study intervention.
3. Prior cholecystectomy surgery (prior appendectomy is acceptable).
4. 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 in Appendix 7).

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.

Laboratory Assessments

10. Presence of hepatitis B surface antigen at screening or within 3 months prior to starting study intervention.
11. Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention.
12. Positive HIV-1 and -2 antigen/antibody immunoassay at screening.
13. ALT >1.5 × upper limit of normal (ULN). A single repeat of ALT is allowed within a single screening period to determine eligibility.
14. 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.
15. Any acute laboratory abnormality at screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
16. Any Grade 2 to 4 laboratory abnormality at screening, with the exception of creatine phosphokinase (CPK), lipid abnormalities (e.g., total cholesterol, triglycerides), and ALT (described above), will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.
17. Urine drug screen positive (showing presence of): amphetamines, barbiturates, cannabinoids, cocaine, or phencyclidine, or nonprescribed opiates, oxycodone, benzodiazepines, methadone, MDMA, methamphetamines, or tricyclic antidepressants at screening or before the first dose of study intervention

Prior/Concomitant Therapy

18. 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 grams/day and topical hydrocortisone cream 1% are permitted for use any time during the study.)
19. Treatment with any vaccine within 30 days prior to receiving study intervention.
20. Unwillingness to abstain from excessive consumption (defined in Section 5.3.1) 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

21. 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).
22. Prior intolerance to GSK3640254, DRV/RTV or ETR in this or another clinical study.
23. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.

Diagnostic assessments

24. Any positive (abnormal) response confirmed by the investigator on a screening clinician- or qualified designee-administered C-SSRS.
25. A sustained supine systolic blood pressure >140 mm Hg or <90 mm Hg or a supine diastolic blood pressure >95 mm Hg or <50 mm Hg at Screening or Check-in . Up to 2 repeats are allowed for confirmation.
26. Any significant arrhythmia or ECG finding (e.g., prior myocardial infarction in the past 3 months, symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained or sustained ventricular tachycardia, any degree of atrioventricular block, or conduction abnormality) which, in the opinion of the investigator or VH/GSK medical monitor, will interfere with the safety for the individual participant.

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

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

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

Other Exclusions

28. History of regular alcohol consumption within 6 months of the study, defined as an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.
29. Unable to refrain from tobacco or nicotine-containing products within 3 months prior to screening.
30. 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

- Abstain from excessive consumption of red wine, grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study. Excessive consumption is defined as more than 1 glass of wine or 8 oz juice or one of these fruits per day, in combination.
- All doses of GSK3640254 and DRV/RTV and ETR in this study will be administered in the fed state. Participants will fast overnight for at least 8 hours before breakfast and prior to the AM dose and for at least 2 hours before dinner and prior to the PM dose. Participants will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of the completion of meal consumption. Participants will not receive any further food until 4 hours post-dose on serial PK sampling days (Days 7, 21, and 31 for Cohorts 1 and 2 and Days 7 and 21 for Cohort 3). The moderate fat meal will contain about 600 calories with approximately 30% of the calories coming from fat.
- A standard lunch will be provided approximately 4 hours after dosing. A standard dinner will be served approximately 10 hours after dosing. The food content of meals must be identical on serial PK sampling days.
- No water is allowed from 1 hour prior to dosing until 1 hour after dosing with GSK3640254 and/or DRV/RTV and ETR drugs (both AM and PM dose) 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, 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 on Day -1 and must abstain from recreational drug use from screening until after the final visit.

5.3.3. Activity

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

5.4. Screen Failures

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

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

5.5. Criteria for Temporarily Delaying

Not applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1. Study Interventions Administered

Intervention Name	GSK3640254	Darunavir	Ritonavir	Etravirine
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strengths	100 mg	600 mg	100 mg	200 mg
Dosage Levels	200 mg	600 mg	100 mg	200 mg
Route of Administration	oral	oral	oral	oral
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Sourced by Sponsor	Sourced by PPD		
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.	In accordance with product label		

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

6.2. Preparation/Handling/Storage/Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

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

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

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

6.7. Treatment of Overdose

For this study, any dose of GSK3640254, DRV/RTV, or ETR 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 of GSK3640254. The investigator will use clinical judgment to treat an overdose.

Human experience of acute overdose with ETR or DRV co-administered with low dose RTV is limited. There is no specific antidote for an overdose with either DRV/RTV or ETR. Treatment of an overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the participant. Since DRV and ETR are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substances.

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, DRV/RTV, or ETR 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 last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the case report form (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.

6.8. Concomitant Therapy

Acetaminophen/paracetamol, at doses of ≤2 grams/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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

7.1.1. Liver Chemistry Stopping Criteria

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

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

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

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

7.1.2. QTc Stopping Criteria

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

- The ECG taken on Day -1 will be a single reading to confirm eligibility. The intra-period pre-dose time point ECGs on Days 1, 12, and 22 for Cohorts 1 and 2 and Day 1 for Cohort 3 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 Cohorts 1 and 2, the pre-dose triplicate ECGs on Days 1, 12, and 22 will serve as the basis for the Baseline QTcF for Periods 1, 2, and 3, respectively. In contrast, in Cohort 3, pre-dose triplicate ECG will only be taken on Day 1.
- An enrolled participant that develops an on-treatment QTcF >500 ms or an increase from Baseline QTcF >60 ms should have 2 repeat unscheduled ECGs within 10 minutes. Using these triplicate ECGs, if the average QTcF >500 ms or an increase from Baseline QTcF >60 ms, the participant will be withdrawn from the study.
- Finally, this participant should have 1) a complete, unscheduled chemistry panel, 2) an unscheduled GSK3640254 PK sample, and 3) repeated unscheduled ECGs until their QTc measurement returns to their original averaged QTcF value at Day 1 pre-dose.

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

7.1.3. Rash/Hypersensitivity Evaluation Criteria

A participant presenting with a Grade 3 AE or higher rash (diffuse macular, maculopapular, OR morbilliform rash with vesicles or limited number of bullae; OR superficial ulcerations of mucous membrane limited to 1 site) or a Grade 2 rash (diffuse macular, maculopapular, or morbilliform rash; OR target lesions) with evidence of systemic involvement will be followed as appropriate until resolution of the AE(s).

7.1.4. Columbia-Suicide Severity Rating Scale Criteria

Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered C-SSRS during the treatment phase of the study 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 intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.5. 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) (Appendix 8) 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, behavioral, or compliance reasons. This is expected to be uncommon.
- A participant who is withdrawn from the study for any reason related to safety (listed in Section 7.1.5 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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for

screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should 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 assessments, vital signs are to be taken first.

8.2.3. Electrocardiograms

- Twelve-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR,

QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

- The ECGs taken on Day -1 will be a single reading to confirm eligibility.
- The intra-period pre-dose 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 Cohorts 1 and 2, the pre-dose triplicate ECGs on Days 1, 12, and 22 will serve as the basis for the Baseline QTcF for Periods 1, 2, and 3, respectively. In contrast, in Cohort 3, pre-dose triplicate ECG will only be taken on Day 1.
- Post-dose ECGs otherwise are single assessments.
- 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 ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed 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 assessments 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 significant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal by the investigator during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

- 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 involvement in the study.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

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

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

Emergent non-suicidal psychiatric AE evaluation and management:

- Any DAIDS Grade 1 or 2 psychiatric AE: A Grade 1 or 2 psychiatric AE may result in additional unscheduled visits (in-clinic or at home) as clinically indicated. This may include a more in-depth assessment of the AE through interview, additional unscheduled clinical laboratory tests, and/or imaging. Psychiatric consultation may be required at the discretion of the investigator. Any pharmacotherapy should be discussed with the medical monitor.
- Any DAIDS Grade 3 or 4 psychiatric AE: As described in Section 7.1.5, 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).

8.2.7. 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 studies 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 studies were representative of, associated with, or resulted from gastric toxicity (if present). Thus, in a clinically conservative fashion 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 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: 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 it is intraperitoneal, extraperitoneal, medication related, infection related, or due to a metabolic disorder [Hasler, 2012]). Medications can cause nausea and vomiting acutely.
Dyspepsia	The investigator should identify the presence of red flags (odynophagia, unexplained weight loss, recurrent vomiting, GI bleeding, jaundice, palpable mass or adenopathy, or family history of GI malignancy). Symptoms of dyspepsia could include early satiety, bloating, or belching. Additionally, atypical symptoms of dyspepsia could include pharyngitis, asthma, bronchitis, hoarseness, chest pain, or abdominal pain.
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: 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., preformation 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.

8.2.8. COVID-19 Measures

The measures approved for implementation within this clinical trial to protect participant safety, welfare, and rights, and to 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, Serious Adverse Events, and Other Safety Reporting

The definitions of 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

(https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf). While the study population will consist of HIV-1 seronegative healthy participants, the DAIDS criteria is being used in later phase clinical studies (e.g., Phase 2); additionally, the DAIDS criteria have a more conservative grading scale relative to other scales (e.g., Common Terminology Criteria for Adverse Events [CTCAE] Version 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).

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 8.3.6) will be followed until the event is resolved, stabilized,

otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 6.

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and through the end of pregnancy (termination or delivery).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to VH/GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. 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.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant /pregnant female partner, and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, 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.

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, or psychiatric) may be defined in the reporting and analysis plan.

8.4. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254, as specified in the SoA (Section 1.3).
- Separate whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of DRV, RTV, and ETR 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 DRV, RTV, and ETR. Samples collected for analyses of plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK3640254 and DRV, RTV, and ETR, any remaining plasma may be analyzed for other compound-related metabolites and the results provided in a separate report.

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

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

Administration of GSK3640254 may change the exposure to DRV/RT and ETR, and administration of DRV/RTV and ETR may change the exposure to GSK3640254.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

As there is no formal research hypothesis being statistically tested in this study, the sample size was not selected based on statistical considerations but determined using feasibility. Per cohort, approximately 16 participants will be enrolled to ensure that 14 evaluable participants complete the study. If participants prematurely discontinue the study, additional participants may be enrolled after consultation with the sponsor to ensure that the required number of evaluable participants complete the study.

Based on the results from previous PK studies for GSK3640254 (GSK Study 207187 and 208131) the coefficient of variability (CVw) ranged from 17 to 38% and 13 to 31%, respectively for AUC0-tau and Cmax. Therefore, it is decided that for GSK3640254 38% would be a conservative estimate on which the sample size calculation is based.

Historical references were used to calculate the CVw for PK parameters of DRV, RTV, and ETR and are provided in Table 2.

Table 2 Historical References for the Sample Size (n) and Intrasubject Coefficient of Variability for Pharmacokinetic Parameters of Darunavir, Ritonavir, and Etravirine

Historical Reference	Analyte	Parameter	n	CVw (%)
Sekar (2010)	Darunavir	AUC(0-tau)	11	34.7
		Cmax	11	40.8
		Cmin	11	54.2
	Ritonavir	AUC(0-tau)	11	26.4
		Cmax	11	20.4
		Cmin	11	40.8
Schöller-Gyüre (2007)	Etravirine (Study C168)	AUC(0-tau)	23	16.3
		Cmax	23	12.1
		Cmin	23	15.4
	Etravirine (Study 178)	AUC(0-tau)	37	9.7
		Cmax	37	10.4

Historical Reference	Analyte	Parameter	n	CVw (%)
		Cmin	37	13.3

CVw = coefficient of variability.

Based upon the historical references [Sekar, 2010; Schöller-Gyüre, 2007] the conservative estimates of CVw chosen for the analytes DRV, RTV, ETR are 54.2%, 40.8%, and 16.3%, respectively.

Administration of GSK3640254 may change the exposure to DRV/RTV and ETR, and administration of DRV/RTV and ETR may change the exposure to GSK3640254; therefore, a range for point estimates (0.9, 1.0, and 1.1) was explored for the treatment differences in terms of geometric mean ratios of PK parameters.

With a sample size of 14 evaluable participants it is estimated that the precision (i.e., half-width of the 90% CI on the log and ratio scale), and CI on the original scale for each point estimate will be:

Drug	CVw (%)	Half-Width (Log Scale)	Half-Width (Original Scale)	Point Estimate	90% CI
GSK3640254	38	0.246	0.279	0.9	(0.704, 1.151)
				1.0	(0.782, 1.279)
				1.1	(0.860, 1.407)
Darunavir	54.2	0.340	0.405	0.9	(0.641, 1.264)
				1.0	(0.712, 1.405)
				1.1	(0.783, 1.545)
Ritonavir	40.8	0.263	0.301	0.9	(0.692, 1.171)
				1.0	(0.769, 1.301)
				1.1	(0.846, 1.431)
Etravirine	16.3	0.108	0.114	0.9	(0.808, 1.003)
				1.0	(0.898, 1.114)
				1.1	(0.987, 1.225)

Abbreviation: CVw = coefficient of variability.

9.2.2. Sample Size Sensitivity

For a sensitivity analysis, assuming a range of within-subject variability and a sample size of 12, 14, and 16 evaluable participants, it is estimated that the precision (i.e., half-width of the 90% CI on the log and ratio scale), and CI on the original scale for each point estimate will be:

Evaluable Participants	CVw (%)	Half-Width (Log Scale)	Half-Width (Original Scale)	Point Estimate	90% CI
12	30	0.215	0.240	0.9	(0.726, 1.116)
				1.0	(0.807, 1.240)
				1.1	(0.887, 1.364)
	40	0.283	0.327	0.9	(0.678, 1.194)
				1.0	(0.754, 1.327)
				1.1	(0.829, 1.460)
	50	0.346	0.413	0.9	(0.637, 1.272)
				1.0	(0.708, 1.413)
				1.1	(0.778, 1.555)
14	30	0.196	0.217	0.9	(0.740 , 1.095)
				1.0	(0.822 , 1.217)
				1.1	(0.904 , 1.338)
	40	0.258	0.294	0.9	(0.695 , 1.165)
				1.0	(0.773 , 1.294)
				1.1	0.850 , 1.424)
	50	0.316	0.372	0.9	(0.656 , 1.234)
				1.0	(0.729 , 1.372)
				1.1	(0.802 , 1.509)
16	30	0.182	0.200	0.9	(0.750, 1.080)
				1.0	(0.834, 1.200)
				1.1	(0.917, 1.320)
	40	0.239	0.270	0.9	(0.709, 1.143)
				1.0	(0.787, 1.270)
				1.1	(0.866, 1.397)
	50	0.293	0.340	0.9	(0.671, 1.206)
				1.0	(0.746, 1.340)
				1.1	(0.821, 1.474)

CI = confidence interval; CVw = coefficient of variability.

For each cohort, approximately 16 participants will be treated to ensure that 14 evaluable participants complete the study.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

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

9.4. Statistical Analyses

9.4.1. Pharmacokinetic Analyses

Plasma GSK3640254 and DRV, RTV, and ETR concentration-time data will be analyzed by PPD, under the oversight of the Clinical Pharmacology Modeling & Simulation Department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher. Statistical analysis will be performed by PPD, under the oversight of Clinical Statistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

Endpoint	Statistical Analysis Methods
Primary	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of GSK3640254 will be subjected to PK analyses using noncompartmental methods. • Based on the individual concentration-time data the following primary plasma PK parameters for GSK3640254 will be estimated: AUC(0-tau) and Cmax • Analysis will be performed to compare the PK exposure of GSK3640254 with and without DRV/RTV (Cohort 1), ETR (Cohort 2), or DRV/RTV/ETR (Cohort 3). Analyses will be performed on the natural logarithms of AUC(0-tau) and Cmax using linear mixed-effect models with treatment as a fixed effect and measurements within participant as repeated measures, and subject as a random effect. Effects will be estimated, and 90% CIs will be constructed for the following treatment comparisons: • Treatment A+B versus Treatment A (Cohort 1) • Treatment A+C versus Treatment A (Cohort 2) • Treatment A+B+C versus Treatment A (Cohort 3) Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale. • Plasma concentrations of DRV, RTV, and ETR will be subjected to PK analyses as described above for GSK3640254. Based on the individual concentration-time data the following plasma PK parameters for DRV, RTV, and ETR will be estimated: AUC(0-tau) and Ctau • Analysis will be performed to compare the PK exposure of DRV (Cohort 1), RTV (Cohort 1), and ETR (Cohort 2) with and without GSK3640254 as described above. Effects will be estimated, and 90% CIs will be constructed for the following treatment comparisons: • Treatment A+B versus Treatment B (Cohort 1) • Treatment A+C versus Treatment C (Cohort 2) Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254, DRV, RTV, and ETR primary PK parameter (AUC[0-tau] and Cmax) values will be summarized by treatment.
Secondary	Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254, DRV, RTV, and ETR secondary PK parameters (Tmax and Ctau) values will be presented. Additionally, pre-dose (trough) PK plasma concentrations of GSK3640254 (Treatment A), DRV/RTV (Treatment B), and ETR (Treatment C) will be summarized and used to assess achievement of steady state.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

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

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

9.4.3. Other Analysis

Additionally, 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 into account applicable regulatory guidance and industry best practices for handling such situations [DHHS, 2020; EMA, 2020a; EMA 2020b].

9.5. Interim Analysis

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse event
ALT	Alanine aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-tau)	Area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state
BID	Twice daily
bpm	Beats per minute
CIB	Clinical Investigator's Brochure
Cmax	Maximum observed concentration
C-QTc	Concentration-corrected QT interval
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
Ctau	Plasma concentration at the end of the dosing interval
CVw	Coefficient of variability
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DRV	Darunavir
ECG	Electrocardiogram
ETR	Etravirine
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
HRT	Hormonal replacement therapy
HTE	HIV-infected treatment-experienced
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
MAD	Multiple ascending dose
MI	Maturation inhibitor
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using the Fridericia formula
QTL	Quality tolerance limits
RTV	Ritonavir
SAD	Single ascending dose
SAE	Serious adverse event
SoA	Schedule of activities
SRM	Study Reference Manual
Tmax	Time of maximum observed concentration
TQT	Thorough QT
ULN	Upper limit of normal
VH	ViiV Healthcare
WOCBP	Woman of childbearing potential

- **Trademark Information**

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
DAIDS
Intelence
Norvir
Phoenix WinNonlin
Prezista
Reyataz

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.

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	Carbon dioxide AST ALT Gamma-glutamyl transferase Total and direct bilirubin Lactate dehydrogenase Total cholesterol Triglycerides	Total protein Albumin Globulin Anion gap Alkaline phosphatase[2] Uric acid Creatine phosphokinase Serum lipase Serum amylase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood, leukocyte esterase, or protein is abnormal)		
Pregnancy testing	• Highly sensitive human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]		
Other Screening Tests	• FSH (as needed in women of non-childbearing potential only) • 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, cannabinoids, cocaine, or phencyclidine, or nonprescribed opiates, oxycodone, benzodiazepines, methadone, or tricyclic antidepressants)		

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), 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.

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.

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.*
▪ Intrauterine device
▪ Intrauterine hormone-releasing system
▪ Bilateral tubal occlusion
▪ Azoospermic partner (vasectomized or due to a to medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview..
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
▪ Sexual abstinence *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*
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. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

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

10.4.1. Regulatory and Ethical Considerations

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

10.4.2. Financial Disclosure

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

10.4.3. Informed Consent Process

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

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

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or his or her 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 the 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 participant, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with VH/GSK Policy.
- VH/GSK intends to make anonymized patient-level data from this 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.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.4.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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.
- Guidance on completion of CRFs will be provided in the electronic CRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study, and deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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).
- Records and documents, including signed ICFs, 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.4.9. Study and Site Start and Closure

First Act of Recruitment

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.

Study/Site Termination

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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, 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 international normalized ratio (INR) >1.5, report as an SAE.
See additional Actions and Follow-up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow-up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to VH/GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within Baseline (see MONITORING below)
MONITORING:
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, 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 colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend
• Obtain blood sample for PK analysis, obtained within 48 hours of last dose[4]
• Serum creatine phosphokinase and lactate dehydrogenase
• Fractionate bilirubin, if total bilirubin ≥2 × ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over-the-counter medications
• Record alcohol use on the liver event alcohol intake CRF
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.
• Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the</td></tr>
</table>

Liver Chemistry Stopping Criteria	
	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 and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.6.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. 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.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT ≥3 × ULN AND total bilirubin ≥2 × ULN (>35% direct bilirubin) or INR >1.5 must be reported as a SAE.

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention 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.
- 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 required form.
- There may be instances when copies of medical records for certain cases are requested by VH/GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to VH/GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- Life-Threatening: Inability to perform basic self-care functions.

An event is defined as "serious" when it meets at least 1 of the 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 submitted documents.

- 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 an 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) 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 Data Collection Tool

- 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 tool 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 resources and operations, site closures, travel limitations and the inability of an individual participant to attend clinic visits, 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 participant 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 to 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 principal investigator 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/IRB/IEC regulations.

10.7.2. COVID-19 Specific Data Capture

10.7.2.1. Capturing COVID-19 Specific Protocol Deviations

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

10.7.2.2. Capturing COVID-19 Specific Adverse Events and Serious Adverse Events

ViiV Healthcare is 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 analyses.

Please use the following guidance:

1. Adverse events 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. Serious AEs 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, reporting, and decisions around the 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 electronic 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.

10.7.2.2.1. World Health Organization Case Definition (March 20, 2020 Version)

Suspected case:

A. A participant 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 participant with any acute respiratory illness AND having been in contact (see definition of "COVID-19 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 participant with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

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

OR

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

Confirmed case:

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

COVID-19 Contact:

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

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

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

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

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DHHS, 2017) is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, CCI are to be classified as **Grade 5.**

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.

11. REFERENCES

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