TITLE PAGE

Protocol Title: A Two-Part, Randomized, Open-Label, Single Dose, Crossover Clinical Study to Assess the Relative Bioavailability of Fixed-Dose Combinations of GSK3640254 and Dolutegravir and to Assess the Effect of Food on the Select Fixed Dose Combination of GSK3640254 and Dolutegravir in Healthy Participants

Protocol Number: 213055

Compound Number or Name: GSK3640254, GSK4107821

Brief Title: A Relative Bioavailability and Food-Effect Study of the Fixed Dose Combination of GSK3640254 and Dolutegravir in Healthy Participants

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

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

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

Regulatory Agency Identifying Number: IND 139,838

Approval Date: 05-MAY-2021

SPONSOR SIGNATORY:

Protocol Title: A Two-Part, Randomized, Open-Label, Single Dose, Crossover Clinical Study to Assess the Relative Bioavailability of Fixed-Dose Combinations of GSK3640254 and Dolutegravir and to Assess the Effect of Food on the Select Fixed Dose Combination of GSK3640254 and Dolutegravir in Healthy Participants

Protocol Number: 213055

Compound Number or Name: GSK3640254, GSK4107821

Max Lataillade, DO, MPH
VP and Head, Global Research Strategy
ViiV Healthcare

Date

The signed page is a separate document.

Medical Monitor Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	*05-May -2021*	*TMF-13328213*
Original Protocol	*25-Mar-2021*	*TMF-11919451*

Amendment 1 [05-May-2021]

Overall Rationale for the Amendment: The primary driver for the protocol amendment was to clarify specific errors which related to the conduct of this protocol before study initiation.

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis	Changed the number of days in Part 1 & Part 2 of this study. Also changed the number of washout days to 7.	The days for participation was previously incorrect & washout was shortened to 7 days.
1.3 Schedule of Activities	Changed he number of screening days	The number of screening days was previously incorrect
1.3 Schedule of Activities	Added Day 7 Safety assessments	Additional safety checks prior to dosing
1.3 Schedule of Activities	Sub-script 1 was changed to reflect a corrected baseline visit, with a 7-day washout.	Washout was changed to 7 days to shorten time between doses.
1.3 Schedule of Activities	Day 5 PK sampling for GSK3640254 & DTG was added as 96h collection timepoints	Day 5 was not included previously, however 96h was reflected correctly.
5.2 Exclusion Criteria	Deleted exclusion # 21 as it was a duplicate of exclusion # 23	Duplicate exclusion criteria
6.1 Study Interventions Administered	Corrected the source of GSK3640254 / DTG formulation as sponsor supplied	DTG was previously listed as “locally sourced” in error

TABLE OF CONTENTS

PAGE

TITLE PAGE 1

SPONSOR SIGNATORY: 2

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3

1. PROTOCOL SUMMARY 7
   - 1.1. Synopsis 7
   - 1.2. Schema 10
   - 1.3. Schedule of Activities (SoA) 11

2. INTRODUCTION 18
   - 2.1. Study Rationale 18
   - 2.2. Background 18
     - 2.2.1. Key Safety Data with a Prior Maturation Inhibitor (GSK3532795) 18
     - 2.2.2. Key Clinical Data on GSK3640254 to date 19
     - 2.2.3. Dolutegravir 20
     - 2.2.4. Drug interaction Potential with GSK3640254 and Dolutegravir 20
   - 2.3. Benefit/Risk Assessment 21
     - 2.3.1. Risk Assessment 22
     - 2.3.2. Benefit Assessment 28
     - 2.3.3. Overall Benefit: Risk Conclusion 28

3. OBJECTIVES AND ENDPOINTS 28

4. STUDY DESIGN 29
   - 4.1. Overall Design 29
   - 4.2. Scientific Rationale for Study Design 30
   - 4.3. Justification for Dose 31
   - 4.4. End of Study Definition 32

5. STUDY POPULATION 32
   - 5.1. Inclusion Criteria 32
   - 5.2. Exclusion Criteria 33
   - 5.3. Lifestyle Considerations 36
     - 5.3.1. Meals and Dietary Restrictions 36
     - 5.3.2. Caffeine, Alcohol, and Tobacco 37
     - 5.3.3. Activity 38
   - 5.4. Screen Failures 38
   - 5.5. Criteria for Temporarily Delaying 38

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY 38
   - 6.1. Study Interventions Administered 38
   - 6.2. Preparation/Handling/Storage/Accountability 39
   - 6.3. Measures to Minimize Bias: Randomization and Blinding 40
   - 6.4. Study Intervention Compliance 40
   - 6.5. Dose Modification 40

6.6. Continued Access to Study Intervention after the End of the Study 40
6.7. Treatment of Overdose 41
6.8. Concomitant Therapy 41

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 41
7.1. Discontinuation of Study Intervention 41
7.1.1. Liver Chemistry Stopping Criteria 42
7.1.2. QTc Stopping Criteria 42
7.1.3. Rash/Hypersensitivity Evaluation Criteria 42
7.1.4. Columbia-Suicide Severity Rating Scale Criteria 43
7.1.5. Individual Participant Laboratory Abnormality and Adverse Event Stopping Criteria 43
7.2. Participant Discontinuation/Withdrawal from the Study 43
7.3. Lost to Follow Up 44

8. STUDY ASSESSMENTS AND PROCEDURES 44
8.1. Efficacy Assessments 45
8.2. Safety Assessments 45
8.2.1. Physical Examinations 45
8.2.2. Vital Signs 45
8.2.3. Electrocardiograms 46
8.2.4. Clinical Safety Laboratory Assessments 46
8.2.5. Pregnancy Testing 47
8.2.6. Suicidal Ideation and Behaviour Risk Monitoring 47
8.2.7. Gastrointestinal Intolerability Evaluation and Monitoring Plan (with Stopping Criteria) 48
8.2.8. COVID-19 Measures 50
8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting 50
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 50
8.3.2. Method of Detecting AEs and SAEs 51
8.3.3. Follow-up of AEs and SAEs 51
8.3.4. Regulatory Reporting Requirements for SAEs 51
8.3.5. Pregnancy 51
8.3.6. Adverse Events of Special Interest 52
8.4. Pharmacokinetics 52
8.5. Genetics 52
8.6. Biomarkers 53
8.7. Immunogenicity Assessments 53
8.8. Medical Resource Utilization and Health Economics 53

9. STATISTICAL CONSIDERATIONS 53
9.1. Statistical Hypotheses 53
9.2. Sample Size Determination 53
9.2.1. Sample Size Assumptions 53
9.2.2. Sample Size Sensitivity 55
9.3. Analysis Sets 56
9.4. Statistical Analyses 56
9.4.1. Pharmacokinetic Analyses 56
9.4.2. Safety Analyses 58

9.4.3. Other Analysis 58
9.5. Interim Analysis 58

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 59
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 59
10.1.1. Regulatory and Ethical Considerations 59
10.1.2. Financial Disclosure 59
10.1.3. Informed Consent Process 60
10.1.4. Data Protection 60
10.1.5. Committees Structure 61
10.1.6. Dissemination of Clinical Study Data 61
10.1.7. Data Quality Assurance 61
10.1.8. Source Documents 62
10.1.9. Study and Site Start and Closure 63
10.1.10. Publication Policy 63
10.2. Appendix 2: Clinical Laboratory Tests 65
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 67
10.3.1. Definition of Adverse Event 67
10.3.2. Definition of Serious Adverse Event 68
10.3.3. Recording and Follow-Up of Adverse Events and Serious Adverse Events 69
10.3.4. Reporting of Serious Adverse Events to VH/GSK 71
10.4. Appendix 4: Contraceptive and Barrier Guidance 73
10.4.1. Definitions: 73
10.4.2. Contraception Guidance: 74
10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments 75
10.6. Appendix 6: COVID-19 Pandemic and Clinical Study Continuity 77
10.6.1. Changes to Study Visits and Study Procedures 77
10.6.2. COVID-19 Specific Data Capture 77
10.7. Appendix 7: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017 80
10.8. Appendix 8: Abbreviations and Trademarks 81

11. REFERENCES 84

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Two-Part, Randomized, Open-Label, Single Dose, Crossover Clinical Study to Assess the Relative Bioavailability of Fixed Dose Combinations of GSK3640254 and Dolutegravir and to Assess the Effect of Food on the Select Fixed Dose Combination of GSK3640254 and Dolutegravir in Healthy Participants

Brief Title: A Relative Bioavailability (BA) and Food-Effect Study of the Fixed Dose Combination (FDC) of GSK3640254 and Dolutegravir (DTG) in Healthy Participants

Rationale: This is a Phase 1, 2-part, randomized, open-label, single-dose, crossover study to compare the relative BA of 2 FDCs of GSK3640254 / DTG with GSK3640254 and DTG administered together as single agents. Data from this study will inform formulation decisions for future clinical studies.

In addition, this study will investigate the effect of food on the pharmacokinetics (PK) of the selected FDC of GSK3640254 / DTG. Most GSK3640254 completed clinical studies to date have been conducted with moderate fat and calorie meals. This study will investigate the effect of a high fat and calorie meal on the PK, safety, and tolerability of the FDC of GSK3640254 / DTG, in comparison with administration under fasting conditions.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part 1 • To assess the relative bioavailability of FDCs of GSK3640254 / DTG compared with GSK3640254 and DTG administered together as single agents when administered with a moderate fat and calorie meal Part 2 • To assess the effect of food on the PK of the selected FDC of GSK3640254 / DTG when administered with a high fat and calorie meal compared to fasted conditions	Parts 1 and 2 • AUC(0-∞), AUC(0-t), and Cmax for GSK3640254 and DTG

Objectives	Endpoints
Secondary	
Part 1 • To assess the safety and tolerability of FDCs of GSK3640254 / DTG compared with GSK3640254 and DTG administered together as single agents Part 2 • To assess the safety and tolerability of selected FDC of GSK3640254 / DTG following single oral administration to healthy participants under fasted or fed conditions	Parts 1 and 2 • Safety and tolerability parameters for AEs or SAEs, observed and change from baseline clinical laboratory assessments, ECGs, and vital sign measurements

AE = adverse event; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the plasma concentration-time curve from time zero to time t; C24 = plasma concentration at 24 hours post-dose; CL/F = apparent oral clearance; Cmax = maximum observed concentration; DTG = dolutegravir; ECG = electrocardiogram; FDC = fixed-dose combination; PK = pharmacokinetics; SAE = serious adverse event; t1/2 = apparent terminal phase half-life; tlag = lag time for absorption; Tmax = time of maximum observed concentration.

Overall Design: This is a Phase 1, 2-part, randomized, open-label, single-dose, crossover study in healthy participants to compare the relative BA of 2 FDCs of GSK3640254 / DTG with GSK3640254 and DTG administered together as single agents (Part 1) and to assess the effect of food on the PK of the selected FDC of GSK3640254 / DTG from Part 1 (Part 2). Participants in both Part 1 and Part 2 will be screened within 35 days before the first dose of study intervention.

Part 1 will consist of a screening period and 3 treatment periods with a single dose of study intervention per treatment period.

Part 2 will consist of a screening period and 2 treatment periods with a single dose of study intervention per treatment period. This will be followed by an End of Study analysis.

In Part 1, Treatments A, B, and C will be administered in the fed state. Participants will fast overnight for at least 10 hours prior to breakfast and will receive a moderate fat and calorie meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing.

Part 2 will be dosed using a formulation selected from Part 1 based on PK data. Treatment D will be administered in the fed state. Participants will fast overnight for at least 10 hours prior to breakfast and will receive a high fat and calorie meal 30 minutes

prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing. Treatment E will be administered in the fasted state. Participants will fast overnight for at least 10 hours prior to dosing and until 4 hours after dosing.

In both Part 1 and Part 2, PK blood samples for the analysis of GSK3640254 and DTG will be collected prior to dosing (0 hour) on Day 1 and up to 96 hours post-dose in each period.

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

Study assessments will be performed as indicated in the Schedule of Activities (SoA; Section 1.3). For Part 1, study participants will be confined to the clinic from Day -2 of Period 1 until discharge on Day 5 of Period 3. For Part 2, study participants will be confined to the clinic from Day -2 of Period 1 until discharge on Day 5 of Period 2.

Brief Summary: A relative BA and food-effect study of the FDC of GSK3640254 / DTG in healthy participants. Study details include:

Part 1:

- Study Duration: 56 days (including screening)
- Treatment Duration: 3 days (Day 1 of each period)

Part 2:

- Study Duration: 49 days (including screening)
- Treatment Duration: 2 days (Day 1 of each period)

Number of Participants: For each part, approximately 18 participants will be enrolled to ensure that 14 evaluable participants complete the study.

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

Intervention Groups and Duration: Participants in Part 1 and Part 2 will be randomly assigned to a treatment sequence prior to dosing on Day 1 of Period 1. Participants will receive each of the following treatments administered as 1 treatment per period:

Part 1 (Treatment sequence ABC, BCA, or CAB):

- Treatment A: A single oral dose of GSK3640254 25 mg (2 x tablets), GSK3640254 100 mg (1 x tablet) and DTG 50 mg (1 x tablet) administered together under moderate fat and calorie conditions (reference)

- Treatment B: A single oral dose of GSK3640254 / DTG, 150 mg / 50 mg (1 x monolayer tablet) FDC administered under moderate fat and calorie conditions

- Treatment C: A single oral dose of GSK3640254 / DTG, 150 mg / 50 mg (1 x bilayer tablet) FDC administered under moderate fat and calorie conditions

Part 2 (Treatment sequence DE or ED):

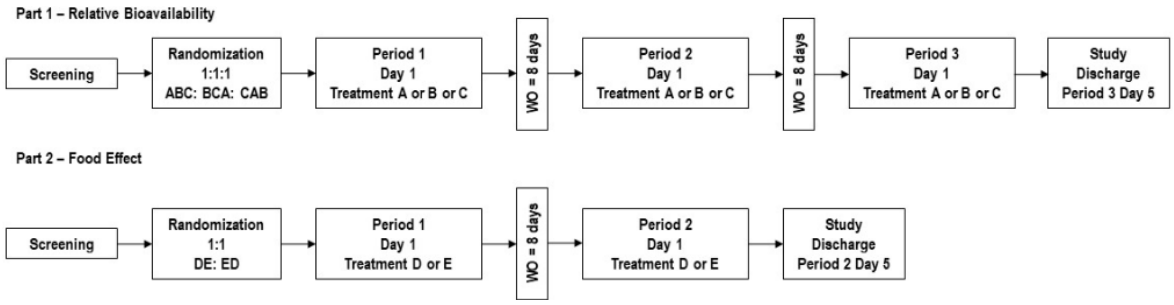
- Treatment D: A single oral dose of selected FDC from Part 1 of GSK3640254 / DTG, 150mg / 50mg administered under high fat and calorie conditions

- Treatment E: A single oral dose of selected FDC from Part 1 of GSK3640254 / DTG, 150 mg / 50 mg administered under fasted conditions

To ensure adequate washout, there will be at least 7 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 7 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

Data Monitoring/ Other Committee: No

1.2. Schema



FDC = fixed dose combination; WO = washout
Treatment A: A single oral dose of GSK3640254 25 mg (2 x tablets), GSK3640254 100 mg (1 x tablet) and DTG 50 mg (1 x tablet) administered together under moderate fat and calorie conditions.
Treatment B: A single oral dose of GSK3640254 / DTG, 150 mg / 50 mg (1 x monolayer tablet) FDC administered under moderate fat and calorie conditions.
Treatment C: A single oral dose of GSK3640254 / DTG, 150 mg / 50 mg (1 x bilayer tablet) FDC administered under moderate fat and calorie conditions.
Treatment D: A single oral dose of selected FDC of GSK3640254 / DTG, 150 mg /50 mg administered under high fat and calorie conditions.
Treatment E: A single oral dose of selected FDC of GSK3640254 / DTG, 150 mg / 50 mg administered under fasted conditions.

1.3. Schedule of Activities (SoA)

- Screening procedures may be completed over more than 1 visit but must all be completed within 35 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 or exclusion criteria.

SCREENING VISIT – PART 1 AND PART 2

Procedure	Screening (up to 35 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 – PART 1

Procedure	Check-in	Baseline[1]	Period 1 & 2				Period 3				Notes
				Washout							
	Day –2	Day -1	Day 1	Day 2	Days 3-5	Days 6-7	Day 1	Day 2	Days 3-4	Day 5[2]	
Admit to clinic	X										
Discharge from clinic										X	Discharge from clinic following completion of the last study procedure on Day 5 of Period 3.
Brief physical examination		X				D7				X	Interim or symptom-targeted physical examination will be performed at the discretion of the investigator. See Section 8.2.1 for description of brief physical examination.
Vital signs		X	X	X	D3	D7	X	X	X	X	Blood pressure and pulse will be measured in triplicate at predose on Day 1 in all periods. Single blood pressure and pulse will be measured on other study days.
Temperature check	X	X	X	X	X	X	X	X	X	X	
12-lead ECG		X	X				X			X	The ECGs on Day 1 in all periods will be taken at predose, and post-dose at 2, 4, and 6 hours. The predose ECGs will be taken in triplicate to establish a baseline QTcF. The post-dose ECGs are single ECGs.
Drug, alcohol, and cotinine screen	X										See Appendix 2 for specific tests to be performed.

Procedure	Check-in	Baseline[1]	Period 1 & 2				Period 3				Notes
	Day –2	Day -1	Day 1	Washout			Day 1	Day 2	Days 3-4	Day 5[2]	
				Day 2	Days 3-5	Days 6-7					
Molecular test for SARS-CoV-2	X*				D5					X	* The second test will be performed on Day -2 after admission to the clinic. Participants will be quarantined within the clinic until the second test result is negative. Once the second test result is confirmed negative, participants can be released into the study unit and will follow infection control practices.
Laboratory assessments (hematology, chemistry, urinalysis)		X[3]		X		D7		X		X	See Appendix 2 for specific tests to be performed. Day 2 samples in each period to be collected 24 hours after dosing.
Pregnancy test	X									X	Serum testing on Day –2
Columbia-Suicide Severity Rating Scale		X				D7				X	
Study intervention: GSK3640254 25 mg, 100 mg or GSK3640254 / DTG 150 mg / 50 mg fixed-dose combination Or DTG 50 mg			X				X				See Section 4.1.
GSK3640254 PK sampling			X	X	D3, D4, D5		X	X	X	X	Blood for PK analysis of GSK3640254 will be collected within 40 minutes prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose in all periods.
Dolutegravir PK sampling			X	X	D3, D4, D5		X	X	X	X	Blood for PK analysis of dolutegravir will be collected within 40 minutes prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose in all periods.

Procedure	Check-in	Baseline[1]	Period 1 & 2				Period 3				Notes
	Day –2	Day -1	Day 1	Washout			Day 1	Day 2	Days 3-4	Day 5[2]	
				Day 2	Days 3-5	Days 6-7					
AE review			←==========X==========→								
SAE review	←==========X==========→										
Concomitant medications	←==========X==========→										

AE = adverse event; D = day; ECG = electrocardiogram; PK = pharmacokinetic; QTcF = QT interval corrected using Fridericia's formula; SAE = serious adverse event.

1 Baseline assessments will be collected on Day -1 before Period 1.

2 Evaluations scheduled for Day 5 in Period 3 will also be performed for participants who discontinue early.

3 Review and approval prior to dosing on Day 1 in Periods 1, 2 and 3.

TIME AND EVENTS – PART 2

Procedure	Check-in	Baseline[Error! Reference source not found.]	Period 1				Period 2				Notes
				Washout							
	Day –2	Day -1	Day 1	Day 2	Days 3-5	Days 6-7	Day 1	Day 2	Days 3-4	Day 5[1]	
Admit to clinic	X										
Discharge from clinic										X	Discharge from clinic following completion of the last study procedure on Day 5 of Period 2.
Brief physical examination		X				D7				X	Interim or symptom-targeted physical examination will be performed at the discretion of the investigator. See Section 8.2.1 for description of brief physical examination.
Vital signs		X	X	X	D3	D7	X	X	X	X	Blood pressure and pulse will be measured in triplicate predose on Day 1 in both periods. Single blood pressure and pulse will be measured on other study days.
Temperature check	X	X	X	X	X	X	X	X	X	X	
12-lead ECG		X	X			D7	X			X	The ECGs on Day 1 in all periods will be taken at predose, and post-dose at 2, 4 and 6 hours. The predose ECGs will be taken in triplicate to establish a baseline QTcF. The post-dose ECGs are single ECGs.
Drug, alcohol, and cotinine screen	X										See Appendix 2 for specific tests to be performed.

Procedure	Check-in	Baseline[Error! Reference source not found.]	Period 1				Period 2				Notes
				Washout							
	Day –2	Day -1	Day 1	Day 2	Days 3-5	Days 6-7	Day 1	Day 2	Days 3-4	Day 5[1]	
Molecular test for SARS-CoV-2	X*				D5					X	* The second test will be performed on Day -2 after admission to the clinic. Participants should be quarantined within the clinic until the second test result is negative. Once the second test result is confirmed negative, they can be released into the study unit and will follow infection control practices.
Laboratory assessments (hematology, chemistry, urinalysis)		X[3]		X		D7		X		X	See Appendix 2 for specific tests to be performed. Day 2 samples in each period to be collected 24 hours after dosing.
Pregnancy test	X									X	Serum testing on Day –2
Columbia-Suicide Severity Rating Scale		X				D7				X	
Study intervention: GSK3640254 / DTG 150 mg / 50 mg fixed-dose combination			X				X				See Section 4.1.
GSK3640254 PK sampling			X	X	D3, D4, D5		X	X	X		Blood for PK analysis of GSK3640254 will be collected within 40 minutes prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose in both periods.
Dolutegravir PK sampling			X	X	D3, D4, D5		X	X	X		Blood for PK analysis of dolutegravir will be collected within 40 minutes prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose in both periods.

Procedure	Check-in	Baseline[Error! Reference source not found.]	Period 1				Period 2				Notes
	Day –2	Day -1	Day 1	Washout			Day 1	Day 2	Days 3-4	Day 5[1]	
				Day 2	Days 3-5	Days 6-7					
AE review			←==========X==========→								
SAE review	←==========X==========→										
Concomitant medications	←==========X==========→										

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

1 Baseline assessments will be collected on Day -1 before Period 1.

2 Evaluations scheduled for Day 5 in Period 2 will also be performed for participants who discontinue early.

3 Review and approval prior to dosing on Day 1 of Periods 1, 2 and 3.

- 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) or 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 healthy authority and the ethics committee before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 1, 2-part, randomized, open-label, single-dose, crossover study to compare the relative bioavailability (BA) of 2 fixed-dose combination (FDCs) of GSK3640254 and Dolutegravir (DTG) with GSK3640254 and DTG administered together as single agents. Data from this study will inform formulation decisions for future clinical studies.

In addition, this study will investigate the effect of food on the pharmacokinetics (PK) of the selected FDC of GSK3640254 + DTG. Most GSK3640254 completed clinical studies to date have been conducted with moderate fat and calorie meal. This study will investigate the effect of a high fat and calorie meal on the PK, safety, and tolerability of the FDC of GSK3640254 + DTG, in comparison with administration under fasting conditions.

2.2. Background

An FDC of GSK3640254 + DTG is being developed for the treatment of patients with human immunodeficiency virus (HIV-1).

Fixed-dose combinations have greatly simplified the treatment of patients with HIV. The promise of improved adherence is important; FDCs potentially allow simplification of dosing and can reduce pill burden. Adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and HIV-1-infected patients who receive antiretroviral therapy rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most patients who struggle with consistent adherence. Thus, an FDC of GSK3640254 + DTG may improve adherence, achieve/maintain virologic suppression and prevent drug resistance.

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

GSK3640254 is a next-generation HIV-1 maturation inhibitor (MI); this novel class of anti-HIV-1 medicines prevents the maturation of HIV-1 virions by binding near a key structural element within the Gag polyprotein that is required for virion maturation and assembly. Laboratory studies confirm that GSK3640254 is an MI with a mechanism of action distinct from current anti-retroviral agents, suggesting little if any risk of cross-resistance to current therapeutic agents.

Key safety data from the Week 24 primary endpoint analysis of a Phase 2b study (205891) of a structurally similar MI, GSK3532795, 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) and a higher rate of nucleoside reverse transcriptase inhibitor resistance (6.5%) with clinically significant changes in GSK3532795 susceptibility was

observed across all 3 GSK3532795 treatment arms [Morales-Ramirez, 2018]. Given these clinical and tolerability issues, ViiV Healthcare (VH) 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 [BMS Document Control Number 930109388] at supratherapeutic doses: 1 healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The 2 participants received 240 mg of GSK3532795 twice daily and 240 mg once daily with food, respectively. These events were assessed as related to study drug but were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric adverse events (AEs) in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia and abnormal dreams). Neither of these GI or psychiatric safety findings have been reproduced in the completed or ongoing clinical trials of GSK3640254 in healthy participants or treatment-naïve participants living with HIV-1.

2.2.2. Key Clinical Data on GSK3640254 to date

A summary of safety data from the completed clinical studies performed to date is summarized here. Note, data from the Phase 2a POC study is preliminary and unvalidated. Prior to a formal report being made available, key findings from this trial are included below and in the dose justification in Section 4.3.

- No deaths or treatment-related SAEs have been reported during clinical studies with GSK3640254.
- Treatment-related dermatologic AEs (including AEs leading to study discontinuation) included rash, drug eruption, pruritis, urticaria, and maculopapular rash. AEs of uticaria and maculopapular rash led to discontinuation.
- Treatment emergent drug-related Grade 2-4 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 volunteer) and 208135 (DDI with oral contraceptive Portia® [Ethinyl Estradiol and Levongestrel], n = 8 healthy volunteers). Subsequent analysis in Study 208135 showed no PK/PD relationship with either GSK3640254 or Portia® and elevated transaminases. The elevated transaminases were likely due to the recent initiation of hormonal contraception in study participants.
- Treatment-related AEs reported in more than 1 study included headache (Studies 207187, 208131, and 208132) and nausea (Studies 207187 and 208132).

- Across trials, the most common AEs regardless of grade, relationship, 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 have been observed: the majority were mild. Both Studies 207187 (MAD) and 208312 (POC) are relevant to this study given dosing of 7-14 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 increase from baseline >60 msec.

A comprehensive description of other clinical data of GSK3640254 can be found in Section 5 of the clinical investigator's brochure (CIB) [GSK Document Number 2018N379610_02] and the supporting clinical study reports (available upon request).

2.2.3. Dolutegravir

Dolutegravir is a potent dual cation binding integrase strand transfer inhibitor, exhibiting rapid reduction in HIV-1 RNA, reasonable efficacy, and a high barrier to resistance. In addition, due to its mechanism of metabolism, DTG lacks many of the frequent drug interactions associated with other medications commonly taken by people living with HIV. To date, the efficacy, PK, safety, and drug interaction potential of DTG has been evaluated in an extensive program of Phase 1 to 3b clinical trials and can be found in the CIB. [GSK Document Number RM2007/00683/14].

Dolutegravir 50 mg tablet is currently approved for marketing in more than 90 countries and in the European Union. Dolutegravir-based regimens have been shown to be a highly effective treatment option for individuals with HIV infection. Dolutegravir50 mg once daily was effective for treatment-naïve and treatment-experienced (integrase inhibitor-naïve) adults [Raffi, 2013; Walmsley, 2013; Clotet, 2014; Buzzi, 2017].

A detailed description of the chemistry, pharmacology, efficacy, and safety of DTG is provided in the CIB [GSK Document Number RM2007/00683/14] and prescribing information [Tivicay, 2020].

2.2.4. Drug interaction Potential with GSK3640254 and Dolutegravir

GSK3640254 has not shown any clinically meaningful impact on the steady state PK of DTG in healthy participants under fed conditions nor has DTG shown any clinically meaningful impact on the steady state PK of GSK3640254 (Study 209712). In addition, no major tolerability findings (including AEs, vital signs, ECG findings, or laboratory values) were noted when GSK3640254 was given in combination with DTG.

GSK3640254 can be administered with DTG without any dose adjustments.

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 QT interval (QT), neuropsychiatric safety, and skin and subcutaneous tissue disorders.

Gastrointestinal intolerability and gastric toxicity (e.g., single-cell parietal cell necrosis) will be assessed using clinical monitoring. Gastric toxicity is not expected following single doses of GSK3640254.

Prolongation of the QT interval is a potential risk. One preclinical study showed 1 dog with an increased QTc interval when given a single dose of GSK3640254. A cardiodynamic analysis of healthy participants in Study 207187 (SAD/MAD) was conducted. A final model from the MAD data showed a QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 msec (90% CI: 1.66 to 9.10) and 6.70 msec (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses (administered with a moderate fat and calorie meal), respectively, on Day 14 (the top 2 doses in the study). Based on this concentration-QTc analysis, a QTcF effect above 10 msec could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately 200 mg once daily). 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 msec or increases >60 msec from baseline. This study contains specific cardiac exclusion criteria (Section 5.2), has ECG monitoring (at Tmax) (Section 1.3), and has QTcF based stopping criteria (Section 7.1.2).

Based on the risk of psychiatric events seen with another MI GSK3532795, (see Section 2.2.1) the protocol will exclude potential participants with any significant pre-existing psychiatric condition or clinical assessment of suicidality based upon 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).

Across clinical studies in participants living with HIV-1 and healthy participants, skin and subcutaneous tissue disorders have been observed (in some cases leading to discontinuation). Participants will be followed regularly for the development of AEs and will undergo physical examinations throughout the study.

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability/reversible gastric toxicity, QT prolongation, skin and subcutaneous tissue disorders, and neuropsychiatric safety), this clinical study will include healthy adult participants.

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_02].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product GSK3640254		
Cardiovascular (QT prolongation)	Non-clinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L‑type calcium channel currents recorded from HEK 293 cells stably transfected with complementary DNA from the ion channels. In a single-dose safety pharmacology study in telemeterized dogs, increases in the QT interval (up to 20 msec) occurred primarily in 1 dog given 17 mg/kg. There were no GSK3640254-related effects on ECG parameters in dogs given up to 25 mg/kg/day for up to 39 weeks. As described earlier, in Study 207187 (MAD) the concentration-QTc analysis, a QTcF effect above 10 msec could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately 200 mg QD). Importantly, in GSK3640254 clinical trials to date, there have been no abnormal clinically significant arrhythmias and no participants have met the study-based stopping criteria for QTcF prolongations: values >500 msec or increases of >60 msec from baseline.	Protocol exclusion criteria based on screening ECG parameters and cardiac medical history (see Section 5.2). Participants will have regular ECG monitoring during the course of the study (see Section 1.3) with QTc stopping criteria (see Section 7.1.2). As noted in Section 7.1.2, if a clinically significant finding is identified (including but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant meets QTc stopping criteria, and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported (at minimum) as an AE.
GI intolerability	Non-clinically, signs of gastrointestinal intolerability (sporadic vomiting and abnormal faeces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. In humans, GI intolerability (predominately abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was evaluated through Phase 2b dosing. While summarized in detail in the CIB, the rates of all GI AEs (all Grade 1 regardless of relationship) in the MAD portion of Study	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms (see Section 5.2). Participants will undergo continuous evaluation for AEs during their participation in the trial; there are clinical stopping criteria based upon intensity of treatment-emergent AEs (see Section 7.1). Additionally, a GI intolerability evaluation and monitoring plan is available to guide the investigator should GI AEs emerge (see Section 8.2.7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	207187 (Phase 1 FTIH) were 33%, 0%, 24%, and 29% in participants who received GSK3640254 50, 100, 200, and 320 mg daily for 14 days (the only completed study with the greatest duration and dose of dosing), respectively (relative to a rate of 21% in participants who received placebo). .	
Gastric toxicity	Gastric toxicity effects on parietal cells and/or chief cells associated with changes in serum gastrin levels were present in preclinical species. These findings were reversible.	It is unclear if gastric toxicity occurs in humans; and if present what the histopathological findings are (whether they correlate with AEs, biomarkers, etc). There is no clinical approach for evaluating gastric toxicity in this study.
Neurologic/psychiatric safety	Two psychiatric SAEs in the previous MI GSK3532795 clinical program (acute psychosis and homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in the TQT study. From a neurologic and psychiatric AE summary and PK/pharmacodynamic analysis for GSK3532795 across all studies, mild 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 demonstrated a similarly low brain distribution/penetration. While summarized in the CIB, the rates of all nervous system and psychiatric AEs in the MAD (Study 207187 FTIH) ranged from	**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 (Section 5.2). Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment and the C-SSRS tool) in participants. Continuous evaluation for AEs during their participation in the trial including direct AE inquiry as noted in Section 1.3. 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 trial and the investigator will arrange for urgent specialist psychiatric evaluation and management.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	24 to 57% and 0 to 17%, respectively, across doses (50 to 320 mg for 14 days) without any trend. No GSK3640254 clinical trial has observed SAEs of acute psychosis or homicidal/suicidal ideation.	Guidance for the management of emergent psychiatric symptoms are available (see Section 8.2.6). There are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 7.1).
Skin and subcutaneous tissue disorders	Across clinical trials, AEs leading to discontinuation have included urticaria and maculopapular rash.	Participants with a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation are excluded. Participants will undergo continuous evaluation for AEs during their participation in the study supplemented by the use of physical examinations. Protocol includes individual participant stopping criteria, 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)
Dolutegravir **Refer to the full prescribing information for additional information on TIVICAY (DTG)**		
Hypersensitivity and rash	Hypersensitivity rash has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase 2b and 3 clinical studies; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme were reported.	Participants with a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation are excluded. Rash and hypersensitivity evaluation criteria are provided in Section 7.1.1. See Section 7.1 for discontinuation of study intervention. The participant ICF includes information on this risk and the actions participants should take in the event of a hypersensitivity reaction or associated signs and symptoms.
Drug induced liver injury (DILI) and other	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered	Participants meeting either of the following criteria during the screening period are excluded from participating (Section 5.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
clinically significant liver chemistry elevations	an uncommon risk for ART containing DTG regardless of dose or treatment population. For participants with hepatitis B virus and/or hepatitis C virus co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for hepatitis B virus co-infected participants, likely contributed to significant elevations in liver chemistries. A review of postmarketing data found that the number of cases reporting particularly severe liver dysfunction was found to be very low in the context of exposure to DTG and DTG/abacavir/lamivudine. The reported cases of severe liver dysfunction (including acute hepatic failure) are complex with potential confounding factors but in a very small number of cases, drug-induced liver injury is likely and the role of DTG-containing regimens cannot be ruled out particularly in those involving DTG.	• ALT ≥1.5 × the ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin >35%). • Positive for HBV (+HBsAg) or positive HCV (positive hepatitis C antibody test) within 3 months of Day 1 of Period 1. Specific/detailed liver chemistry stopping criteria are provided (Section 7.1.1).
Theoretical serious drug interaction with dofetilide	Co-administration of DTG may increase dofetilide plasma concentration via inhibition of organic cation transporter 2 transporter, resulting in potentially life-threatening toxicity.	Concomitant medications (e.g., dofetilide) are prohibited in the study (Section 5.2 and Section 6.8).
Renal function	Mild elevations of creatinine have been observed with DTG that are related to a benign effect on creatinine secretion with blockade of the octamer transcription factor-2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate or effective renal plasma flow.	Participants with a creatinine clearance <60 mL/min are excluded (Section 5.2). Increases in serum creatinine are not expected to have any adverse effect and will reverse during the wash out period after each single dosing of DTG, and; therefore, do not require mitigation in this protocol for DTG.
Psychiatric disorders	Psychiatric disorders including suicidal ideation and behaviors are common in people living with HIV. Events of suicidal ideation, attempt, behavior and completion were observed in clinical studies of DTG, primarily in participants with a pre-existing history of depression or other psychiatric illness.	**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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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). There are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 7.1).
Neural tube defects	In a birth outcome surveillance study in Botswana there have been 7 cases of neural tube defects reported in 3,591 deliveries (0.19%) to mothers taking DTG-containing regimens from the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-DTG-containing regimens from the time of conception (prevalence difference 0.09%; 95% CI 0.03, 0.30). In the same study, no increased risk of neural tube defects was reported in women who started DTG during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started DTG during pregnancy had a neural tube defect, compared with 5 out of 6,748 deliveries (0.07%) to mothers who started non-DTG-containing regimens during pregnancy.	Women who are pregnant will be excluded from the study (Section 5.1). Females of childbearing potential are required to have a negative pregnancy test at both screening and Day 1 of the study and agree to use one of the methods documented in Appendix 4 to avoid pregnancy during the study. Pregnant women will be withdrawn from this study and their pregnancy followed to determine outcome (including premature termination) and status of mother and child.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	A causal relationship of these events to the use of DTG has not been established. The incidence of neural tube defects in the general population ranges from 0.5 to 1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to DTG at the time of conception and in early pregnancy. Data analyzed to date from other sources including the antiretroviral pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with DTG. More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes. In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified. Dolutegravir was shown to cross the placenta in animals.	

AE = adverse event; ALT = alanine aminotransferase; ART = antiretroviral therapy; AUC = area under the plasma concentration-time curve; CPK = creatinine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DTG = dolutegravir; ECG = electrocardiogram; FTIH = first time in human; GI = gastrointestinal; HBV = hepatitis B virus; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; ms = millisecond; HIV = human immunodeficiency virus; PK = pharmacokinetic; QD = once daily; QTc = corrected QT interval; QTcF = corrected QT interval using Fridericia's formula; SAD = single ascending dose; SoA = schedule of activities; TQT = thorough QT; ULN = upper limit of normal.

2.3.2. Benefit Assessment

This is a study in healthy participants and as such there is no expected benefit to administration of GSK3640254 or DTG.

2.3.3. Overall Benefit: Risk Conclusion

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

Dolutegravir is frequently used in HIV clinical practice and has a well-characterized and acceptable safety profile. Given that only healthy participants will be enrolled and that participants will be confined to a clinical facility after dosing, the safety risk of participation in this study is expected to be low. To minimize risk further, the protocol contains exclusions relevant to the study intervention.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Part 1 • To assess the relative bioavailability of FDCs of GSK3640254 / DTG compared with GSK3640254 / DTG administered together as single agents when administered with a moderate fat and calorie meal Part 2 • To assess the effect of food on the PK of the selected FDC of GSK3640254 / DTG when administered with a high fat and calorie meal compared to fasted conditions	Parts 1 and 2 • AUC(0-∞), AUC(0-t), and Cmax for GSK3640254 and DTG
Secondary	
Part 1 • To assess the safety and tolerability of FDCs of GSK3640254 / DTG compared with GSK3640254 / DTG administered together as single agents Part 2	Parts 1 and 2 • Safety and tolerability parameters for AEs or SAEs, observed and change from baseline clinical laboratory assessments, ECGs, and vital sign measurements

Objectives	Endpoints
• To assess the safety and tolerability of selected FDC of GSK3640254 / DTG following single oral administration to healthy participants under fasted or fed conditions	

AE = adverse event; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the plasma concentration-time curve from time zero to time t; C24 = plasma concentration at 24 hours post-dose; CL/F = apparent oral clearance; Cmax = maximum observed concentration; DTG = dolutegravir; ECG = electrocardiogram; FDC = fixed-dose combination; PK = pharmacokinetics; SAE = serious adverse event; t1/2 = apparent terminal phase half-life; Tmax = time of maximum observed concentration.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, 2-part, randomized, open-label, single-dose, crossover study in healthy participants to compare the relative BA of 2 FDCs of GSK3640254 /DTG , 150 mg/50 mg with GSK3640254 / DTG, 150 mg/ 50 mg administered together as single agents (Part 1) and to assess the effect of food on the PK of the selected FDC of GSK3640254 / DTG from Part 1 (Part 2). Participants in both Part 1 and Part 2 will be screened within 35 days before the first dose of study intervention.

Part 1 will consist of a screening period and 3 treatment periods with a single dose of study intervention per treatment period.

Part 2 will consist of a screening period and 2 treatment periods with a single dose of study intervention per treatment period. This will be followed by an End of Study analysis.

Participants will be randomly assigned to receive treatment sequence ABC, BCA or CAB in 1:1:1 ratio in Part 1 and treatment sequence DE or ED in 1:1 ratio in Part 2. Participants will receive each of the following treatments administered as 1 treatment per period:

Part 1 (Treatment Sequence ABC, BCA, or CAB):

- Treatment A: A single oral dose of GSK3640254 25 mg (2 x tablets), GSK3640254 100 mg (1 x tablet), and DTG 50 mg (1 x tablet) administered together under moderate fat and calorie conditions (reference)

- Treatment B: A single oral dose of GSK3640254 / DTG, 150 mg / 50 mg (1 x monolayer tablet) FDC administered under moderate fat and calorie conditions

- Treatment C: A single oral dose of GSK3640254 / DTG, 150 mg / 50 mg (1 x bilayer tablet) FDC administered under moderate fat and calorie conditions

Treatments A, B, and C will be administered in the fed state. Participants will fast overnight for at least 10 hours prior to breakfast and will receive a moderate fat and calorie meal 30 minutes prior to dosing (Section 5.3.1). Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing.

Part 2 (Treatment Sequence DE or ED):

- Treatment D: A single oral dose of selected FDC from Part 1 of GSK3640254 / DTG, 150 mg / 50 mg administered under high fat and calorie conditions

- Treatment E: A single oral dose of selected FDC from Part 1 of GSK3640254 / DTG, 150 mg / 50 mg administered under fasted conditions

Treatment D will be administered in the fed state. Participants will fast overnight for at least 10 hours prior to breakfast and will receive a high fat and calorie meal 30 minutes prior to dosing (Section 5.3.1). Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing. Treatment E will be administered in the fasted state. Participants will fast overnight for at least 10 hours prior to dosing and until 4 hours after dosing.

In both Part 1 and Part 2, PK blood samples for the analysis of GSK3640254 and DTG will be collected prior to dosing (0 hour) on Day 1 and up to 96 hours post-dose in each period (Section 1.3).

Safety and tolerability will be assessed by monitoring and recording of AEs and SAEs, 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). For Part 1, study participants will be confined to the clinic from Day –2 of Period 1 until discharge on Day 5 of Period 3. For Part 2, study participants will be confined to the clinic from Day –2 of Period 1 until discharge on Day 5 of Period 2.

4.2. Scientific Rationale for Study Design

This is a Phase 1, 2-part, randomized, open-label, single-dose, crossover study to compare the relative BA of 2 FDCs of GSK3640254 and DTG with GSK3640254 and DTG administered together as single agents. In addition, this study will investigate the effect of food on the PK of the selected FDC of GSK3640254 + DTG.

Most GSK3640254 completed clinical studies to date have been conducted with moderate fat and calorie meal. Part 2 of this study will investigate the effect of high fat and calorie meals on the PK, safety, and tolerability of the FDC of GSK3640254 + DTG, in comparison with administration under fasting conditions in accordance with the Food and Drug Administration (FDA) guidance for industry on food-effect BA and fed bioequivalence [DHHS, 2002].

The open-label crossover design of this study will specifically evaluate the relative BA of different FDC forms and for studying the effect of food on BA. Random assignment to treatment sequences is an attempt to prevent bias. The washout of at least 7 days between each dose of study intervention should eliminate the possibility of carryover of drug exposure from the previous dose.

This study is participant to the appropriate regulatory and ethics committee approval and will be listed on the website ClinicalTrials.gov. No blinding or placebo control will be used, as these are not necessary for the purposes of this study.

4.3. Justification for Dose

The therapeutic dose range of GSK3640254 being studied in HIV-1 infected adults is 100 to 200 mg (Study 208379, GSK Document Number 2019N399207_03). The dose of 150 mg GSK3640254 was selected for this study as this is below the maximum projected clinically therapeutic dose of GSK3640254. The highest GSK3640254 dose given with a moderate fat and calorie meal was 400 mg. The high fat and calorie meal may increase BA compared with moderate fat and calorie meal but will be below 400 mg SD dosed with moderate fat and calorie meal. The FDC of 150 mg GSK3640254 + 50 mg DTG strength is the starting dose that is a reasonable estimate of the GSK3640254 dose, based on current data. Furthermore, coadministration of DTG (50 mg) and GSK3640254 (200 mg) resulted in no clinically meaningful difference in the steady-state systemic exposure of GSK3640254 compared to GSK3640254 administered alone with geometric least squares mean ratios of 1.04, 0.991, and 0.996 for AUC(0-τ), Cmax, and Cτ, respectively [GSK Document Number 2019N399318_00]. The apparent terminal phase half-life (t1/2) of GSK3640254 was approximately 22 hours in the MAD portion of Study 207187 at the 200-mg dose [GSK document number 2020N430256_00]. To ensure adequate washout, there will be at least 7 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 7 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

The US FDA-approved dose of DTG for treatment naive HIV-infected adult and pediatric patients 12 years and older (and ≥40 kilogram) is 50 mg once daily. Dolutegravir has low to moderate interparticipant PK variability, a predictable exposure-response relationship, and a 14-hour plasma T1/2. Although coadministration of DTG with low-, moderate-, and high-fat and calorie meals in Study ING113674 [GSK Document Number 2010N105142_00] increased DTG exposures (AUC[0-∞]) by 33%, 41%, and 66%, respectively, the TIVICAY® product label states that the approved dose regimen is 50 mg once daily taken with or without food based on efficacy and safety results of Phase 3 studies where DTG was taken without regard to meal times. Furthermore, coadministration of DTG (50 mg) and GSK3640254 (200 mg) resulted in no clinically meaningful difference in the steady-state systemic exposure of DTG compared to DTG administered alone with geometric least squares mean ratios of 1.17, 1.09, and 1.24 for AUC(0-τ), Cmax, and Cτ, respectively [GSK Document Number 2019N399318_00]. Dolutegravir is available as the single entity product TIVICAY and as a component of other FDCs.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he or she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

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 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG).

Weight

3. Body weight ≥50.0 kg (110 lbs) for males and ≥45 kg (99 lbs) for females and body mass index within the range 18.5 to 35.0 kg/m^2 (inclusive).

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

b. Female Participants:

i. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin test), not lactating or breastfeeding, and at least 1 of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

OR

- Is a WOCBP and using a nonhormonal contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4, for 30 days before study intervention, during the treatment periods, and for at least 28 days after the last dose of study intervention and completion of the follow up visit. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

ii. A WOCBP must have a negative highly sensitive serum pregnancy test (Appendix 2) at screening and check-in (Day -2).

iii. Additional requirements for pregnancy testing during and after study intervention are outlined in Appendix 4.

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 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

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

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. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN). A single repeat of ALT is allowed within a single screening period to determine eligibility.
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. Estimated serum creatinine clearance (using Chronic Kidney Disease-Epidemiology Collaboration equation) <60 mL/min.
16. Any acute laboratory abnormality at screening which, in the opinion of the investigator or medical monitor, should preclude participation in the study of an investigational compound.
17. Any Division of Aids (DAIDS) 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.

18. 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 or Concomitant Therapy

19. Unable to refrain from the use of prescription (i.e., dofetilide) 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.)
20. Exposure to an experimental drug, human blood product, monoclonal antibody, or vaccine (which does not have emergency, conditional, or standard market authorization) within 28 days prior to the first dose of study treatment;

    Note: Consult with the Medical Monitor if clarification is needed. Receipt of a SARS-CoV-2 vaccine that has received emergency, conditional, or standard market authorization is allowed if the PI determines that the benefit-risk profile for that individual study participant is favourable. The use of other investigational COVID vaccines that have not received emergency, conditional, or standard market authorization and are still only used in clinical trials will not be allowed at this time.
21. 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 or Concurrent Clinical Study Experience

22. 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).
23. Current enrollment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study intervention (including an investigational COVID vaccine) or any other type of medical research.
24. Prior exposure to GSK3640254 or prior intolerance to DTG in this or another clinical study.
25. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.

Diagnostic assessments

26. Any positive (abnormal) response confirmed by the investigator on a screening clinician- or qualified designee-administered C-SSRS.
27. A sustained supine systolic blood pressure >140 mm Hg or <90 mm Hg or a supinediastolic blood pressure >95 mm Hg or <50 mm Hg at Screening or Check-in . Up to 2 repeats are allowed for confirmation.
28. 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.
29. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

Heart rate[1]	<50 or >100 bpm
PR interval	>200 msec
QRS interval	>110 msec
QTc[2]	>450 msec

1 A heart rate from 101 to 110 beats per minute (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 VH/GSK medical monitor's over-read can supersede that of the machine at any time.

Other Exclusions

30. 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.
31. Unable to refrain from tobacco or nicotine-containing products within 3 months prior to screening.
32. History of sensitivity to any of the study interventions, 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

- Refrain 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 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.

- Once in the clinical unit, participants will not be allowed to eat anything other than the food provided by the clinical unit.
- An evening meal and/or snack, identical across each period, will be provided by the unit (e.g. on Day -1).
- Participants will fast overnight for at least 10 hours prior to breakfast.
- Room temperature water will be provided with dosing (~240 mL, 8 fluid ounces) and at all times except 1 hour predose through 2-hours post-dose. The full 240 mL must be consumed at dosing.
- No food is allowed for at least 4 hours post-dose.
- 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.

5.3.1.1. Fed Conditions

- Treatments A, B, C, and D will be administered in the fed state.
- Participants will fast overnight for at least 10 hours prior to breakfast.
- Treatments A, B, and C will receive a moderate fat and calorie meal.
- The moderate fat and calorie meal will contain about 600 calories with approximately 30% of the calories coming from fat [DHHS, 2002].
- Treatment D (selected from Part 1) will receive a high fat and calorie meal.
- The high fat and calorie meal will contain about 800 to 1000 calories with approximately 50% of the calories coming from the fat [DHHS, 2002].
- Participants will start the 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.

5.3.1.2. Fasted Conditions

- Treatment E (selected from Part 1) will be administered in the fasted state.
- Subjects must fast from all food and drink (except water) for 10 hours prior to dosing and until 4 hours post-dose.

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 follow-up visit.

- Participants must have a negative drug test at screening and on Day -2 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 INTERVENTIONS 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

In Part 1, all 3 treatments will be administered as per randomized treatment sequence. Based on Part 1 interim analysis, a treatment will be selected for administration in Part 2.

Treatment	**A**	**A**	**B**	**C**
Intervention Name	**GSK3640254**	**DTG**	**GSK3640254 / DTG (GSK4107821)**	**GSK3640254 / DTG (GSK4107821)**
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet

Treatment	**A**	**A**	**B**	**C**
Unit Dose Strength(s)	GSK3640254 25mg, 100 mg	DTG 50 mg	GSK3640254 / DTG, 150 mg/50 mg	GSK3640254 / DTG, 150 mg/50 mg
Dosage Level(s)	Single dose of 2 x GSK3640254 25mg Tablets + 1 x GSK3640254 100mg Tablet	DTG 50 mg	Single dose of 1 x GSK3640254 / DTG Tablet	Single dose of 1 x GSK3640254 / DTG Tablet
	Administered together as a single dose			
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	GSK3640254 Sourced by Sponsor	DTG Sourced Locally	GSK3640254 / DTG Sourced by Sponsor	GSK3640254 / DTG Sourced by Sponsor
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.	30 tablets in a HDPE bottle labelled per country requirement	Provided in bulk by GSK. The investigator will package in high density polyethylene bottles. Each bottle will be labeled as required per country requirement.	Provided in bulk by GSK. The investigator will package in high density polyethylene bottles. Each bottle will be labeled as required per country requirement.

DTG = dolutegravir; FDC = fixed-dose combination; 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 either will 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 will be randomly assigned to a treatment sequence in accordance with the randomization schedule generated by PPD prior to the start of the study and using validated software.

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 or DTG 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 or DTG greater than the planned dose within a 24-hour time period (±2 hours) will be considered an overdose.

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

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE or SAE and laboratory abnormalities until GSK3640254 or DTG 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 electronic case report form (eCRF).

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

Participants must abstain from taking prescription (i.e. dofetilide) or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

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 eCRF. 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 and follow-up and for any further evaluations that need to be completed.

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

Discontinuation of study intervention for abnormal liver tests is required when a participant has an ALT ≥3 × ULN or 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. In each study period, the Day 1 pre-dose timepoint will have triplicate averaged QTcF (over a brief approximately 5 to 10 minute recording period). This pre-dose triplicate averaged QTcF value will serve as the baseline for the applicable study period.
- A randomized participant that develops an on-treatment QTcF >500 msec or an increase from baseline QTcF >60 msec should have 2 repeat unscheduled ECGs within 10 minutes. Using these triplicate ECGs, if the average QTcF >500 msec or an increase from baseline QTcF >60 msec, the participant will be withdrawn from the study.
- Finally, this participant should have a completed, unscheduled chemistry panel, an unscheduled GSK3640254 PK sample, and repeated unscheduled ECGs until their QTcF measurement returns to their original averaged QTcF value at Day 1 predose.

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 DAIDS Grade 3 AE or higher rash (CCI [redacted] CCI [redacted] OR CCI [redacted] OR CCI [redacted]) or a DAIDS Grade 2 rash CCI [redacted]; OR CCI [redacted]) with evidence of systemic involvement study medication should be permanently discontinued and 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 DAIDS Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management.

See 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
- DAIDS Grade 3 or higher rash or DAIDS 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 (suspect, probable, or confirmed using the most recent version of the WHO case definition) (Appendix 6) or by laboratory testing. 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 or 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 or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, 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. The site will follow their standard process for repeating vital signs, as needed.

- 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 eCRF.
- 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 ECG 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 pre-dose time point ECGs will generate a triplicate averaged QTcF. This pre dose triplicate averaged QTcF value will serve as the baseline for the applicable study period.
    - 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 eCRF.
- 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.

8.2.4. Clinical Safety Laboratory Assessments

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

8.2.6. Suicidal Ideation and Behaviour Risk Monitoring

GSK3640254 is not a central nervous system active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with a previous MI compound, GSK3532795, all participants will undergo screening using the C-SSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator will exclude them from participating. 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 DAIDS 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 DAIDS 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 DAIDS 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 animals 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 DAIDS 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.

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 study to protect participant safety, welfare, and rights, and to ensure data integrity and the integrity of the clinical study, as a result of COVID-19 only, are outlined in Appendix 6.

8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting

The definitions of AE or SAEs can be found in Appendix 3.

Adverse events will be reported by the participant.

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 all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

The intensity of AEs and laboratory abnormalities will be graded using the most recent version of the DAIDS grading table at the time of last participant last visit (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf). While the study population will consist of 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.

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 recorded as Medical History/Current Medical Conditions not as AEs.

- 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 3. 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 information on 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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.3.6)], will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

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, IRB/IEC, 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.

- 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 and skin disorders) may be defined in the reporting and analysis plan.

8.4. Pharmacokinetics

- Whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of GSK3640254 and DTG as specified in the SoA (Section 1.3).
- A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3640254 and DTG. Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5. Genetics

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 the 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.

9.2. Sample Size Determination

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. For each part, approximately 18 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.

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

9.2.1. Sample Size Assumptions

Based on the results from a previous study ING113674 the intersubject coefficient of variation (CVb) for DTG was 27-34% and 30-35%, respectively, for AUC(0-∞) and Cmax in the fasted state and 31-35% and 19-24%, respectively in the fed state. Based on the results from a previous study 213567 the intersubject coefficient of variation (CVb) for GSK3640254 was 40.3% and 45.3%, respectively, for AUC(0-τ) and Cmax in the fasted state, and 42.2% and 35.6%, respectively in the fed state.

It was assumed that intrasubject coefficient of variation (CVw) was approximately 60% of the calculated CVb. Thus, it was decided that a conservative CVw estimate of 21% would be used for the sample size calculation for DTG and 27.2% would be a conservative estimate to use for the sample size calculation of GSK3640254.

Since it was expected that coadministration of GSK3640254 and DTG would increase the exposure of DTG, a range for point estimate for a ratio of 1.0, 1.1, and 1.2 were explored. It was expected that coadministration of GSK3640254 with DTG would have no significant impact on the exposure of GSK3640254, thus a range for point estimate for a ratio of 0.9, 1.0, and 1.1 were explored.

For DTG, with a sample size of 14, 16 and 18 evaluable participants, it was estimated that the precision (i.e., half-width of the 90% confidence interval [CI] on the log and ratio scale) and CI on the original scale for each point estimate would be as follows:

N	Drug	CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
14	DTG	21	0.139	0.149	1.0	(0.87, 1.15)
					1.1	(0.96, 1.26)
					1.2	(1.04, 1.38)
16	DTG	21	0.128	0.137	1.0	(0.88, 1.14)
					1.1	(0.97, 1.25)
					1.2	(1.06, 1.36)
18	DTG	21	0.120	0.127	1.0	(0.89, 1.13)
					1.1	(0.98, 1.24)
					1.2	(1.06, 1.35)

For GSK3640254, with a sample size of 14, 16 and 18 evaluable participants, it was 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 would be as follows:

N	Drug	CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
14	GSK3640254	27.2	0.179	0.196	0.9	(0.75, 1.08)
					1.0	(0.84, 1.20)
					1.1	(0.92, 1.32)
16	GSK3640254	27.2	0.166	0.181	0.9	(0.76, 1.06)
					1.0	(0.85, 1.18)
					1.1	(0.93, 1.30)
18	GSK3640254	27.2	0.155	0.168	0.9	(0.77, 1.05)
					1.0	(0.86, 1.17)
					1.1	(0.94, 1.28)

9.2.2. Sample Size Sensitivity

For a sensitivity analysis, assuming a range of within-participant variability, a sample size of 14, 16 and 18 evaluable participants, it was 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 would be as follows:

N	Drug	CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% CI
14	Dolutegravir or GSK3640254	30	0.196	0.217	0.9	(0.74, 1.09)
					1.0	(0.82, 1.22)
					1.1	(0.90, 1.34)
					1.2	(0.99, 1.46)
		35	0.228	0.256	0.9	(0.72, 1.13)
					1.0	(0.80, 1.26)
					1.1	(0.88, 1.38)
					1.2	(0.96, 1.51)
16	Dolutegravir or GSK3640254	30	0.182	0.200	0.9	(0.75, 1.08)
					1.0	(0.83, 1.20)
					1.1	(0.92, 1.32)
					1.2	(1.00, 1.44)
		35	0.211	0.235	0.9	(0.73, 1.11)
					1.0	(0.81, 1.23)
					1.1	(0.89, 1.36)
					1.2	(0.97, 1.48)
18	Dolutegravir or GSK3640254	30	0.170	0.185	0.9	(0.76, 1.07)
					1.0	(0.84, 1.19)
					1.1	(0.93, 1.30)
					1.2	(1.01, 1.42)
		35	0.197	0.218	0.9	(0.74, 1.10)
					1.0	(0.82, 1.22)
					1.1	(0.90, 1.34)
					1.2	(0.99, 1.46)

Approximately 18 participants were planned to be treated to ensure that 14 evaluable participants completed the study.

9.3. Analysis Sets

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

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

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Pharmacokinetic Analyses

Plasma GSK3640254 and DTG concentration-time data will be analyzed by PPD, under the oversight of the Clinical Pharmacology Modeling & Simulation Department within VH/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, VH/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

Endpoint	Statistical Analysis Methods
	Population. Plasma concentrations of GSK3640254 and DTG will be subjected to PK analyses using noncompartmental methods. • Based on the individual concentration-time data the following primary plasma PK parameters will be estimated: o AUC(0-∞), AUC(0-t), and Cmax • Analysis will be performed to compare the relative BA of 2 FDCs of GSK3640254 and DTG with GSK3640254 and DTG administered together as single agents. Analyses will be performed on the natural logarithms of AUC(0-∞), AUC(0-t), and Cmax using linear mixed-effect models with treatment, period, and sequence as fixed effects and participant as a random effect. Effects will be estimated, and CIs will be constructed for the following treatment comparison: o Treatment B versus Treatment A o Treatment C versus Treatment A Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale. • The effect of food (moderate fat and calorie meal) on the PK of the select FDC of GSK3640254 + DTG will be similarly analyzed for the following treatment comparisons: o Treatment D versus Treatment E • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 and DTG primary PK parameter values will be summarized by treatment.
Secondary	• Based on the individual concentration-actual time data the following secondary plasma PK parameters will be estimated: o Tmax, tlag, t1/2, and CL/F • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 and DTG secondary PK parameter values will be summarized by treatment. • Summary statistics (arithmetic mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma GSK3640254 and DTG PK concentrations will be summarized by treatment using the PK Concentration Population.

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 VH/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, 2002; EMA, Mar 2020; EMA, Apr 2020].

9.5. Interim Analysis

There will be no formal interim analysis. An analysis is planned after completion of Part 1 and will inform FDC formulation to include in Part 2. Preliminary safety & PK data will be analyzed by PPD under the oversight of Clinical Pharmacology Modeling & Simulation within VH/GSK.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable),), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his or her representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements (HIPAA), 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 their 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 DTG or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3640254 or DTG 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 authorised 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 signature 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.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his 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.

10.1.5. Committees Structure

Not applicable.

10.1.6. 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, VH/GSK intends to make anonymized participant-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- VH/GSK intends to make anonymized patient-level data from this study 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 study 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.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF 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 eCRF.
- Guidance on completion of eCRFs will be provided in 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 and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (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. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final clinical study report or 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.

10.1.8. 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 eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the SRM.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.

10.1.9. 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 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 or no recruitment of participants (evaluated after a reasonable amount of time) 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.

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count Red Blood Cell Count Hemoglobin Hematocrit	Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Absolute neutrophil count
Clinical Chemistry[1]	Blood urea nitrogen Creatinine Glucose (fasting) Potassium Sodium Calcium Chloride Phosphorus	Carbon dioxide Aspartate aminotransferase (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]		

Laboratory Assessments	Parameters
Other Screening Tests	• Molecular test for SARS-CoV-2 (Two consecutive approved molecular tests [polymerase chain reaction or antigen test]. The first test should be performed ≥7 days prior to admission and the second test will be performed on Day -2 after admission to the clinic. • Follicle-stimulating hormone (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: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event

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 intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of Serious Adverse Event

An SAE is defined as any serious adverse event 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 an 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. o 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.

10.3.3. Recording and Follow-Up of Adverse Events and Serious Adverse Events

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 latest version of DAIDS grading table (Appendix 7) 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 predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

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

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by VH/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide VH/GSK with a copy of any post-mortem 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.

10.3.4. Reporting of Serious Adverse Events to VH/GSK

SAE Reporting to VH/GSK via Electronic Data Collection Tool

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

SAE Reporting to VH/GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. 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.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[a] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine device
• 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[a] 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).

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3 × ULN
If ALT ≥3 × ULN AND bilirubin[1,2] ≥2 × ULN (>35% direct bilirubin) or INR >1.5, report as an SAE.
See additional Actions and Follow-up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow-up Assessments</th></tr>
<tr><th>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 eCRF, 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</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 eCRF
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</td></tr>
</table>

Liver Chemistry Stopping Criteria	
assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	total immunoglobulin G or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRF.

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 eCRF. 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: COVID-19 Pandemic and Clinical Study 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 study database.

This appendix outlines the measures which are approved for implementation within this clinical study, to protect participant safety, welfare, and rights, and to ensure data integrity and the integrity of the clinical study, 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.

10.6.1. 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 or 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.

10.6.2. COVID-19 Specific Data Capture

10.6.2.1. Capturing COVID-19 Specific Protocol Deviations

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

10.6.2.2. 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 studies. 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 eCRF will be included 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 eCRF templates to help you collect this information for all COVID-19 related AEs/SAEs.

10.6.2.2.1. World Health Organization Case Definition (December 16, 2020 Version)

Please see the WHO Case Definition for Suspected, Probable, or Confirmed case of SARS-CoV-2 infection: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

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.

10.7. Appendix 7: 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.

10.8. Appendix 8: Abbreviations and Trademarks

AE	Adverse event
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time t
AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BA	Bioavailability
bpm	Beats per minute
CI	Confidence interval
CIB	Clinical Investigator's Brochure
Cmax	Maximum observed concentration
$C\tau$	Trough concentration
C-QTc	Concentration-corrected QT interval
CL/F	Apparent oral clearance
COVID-19	Coronavirus disease
CPK	Creatinine phosphokinase
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CVb	Intersubject coefficient of variation
CVw	Intrasubject coefficient of variation
D	Day
DAIDS	Division of AIDS
DILI	Drug induced liver injury
DTG	Dolutegravir
ECG	Electrocardiogram
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle-stimulating hormone
FTIH	First time in human
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBV	Hepatitis B virus

HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
hCG	Human chorionic gonadotropin
hERG/Ikr	Human Ether-a-go-go-Related Gene/Rapid Delayed rectifier
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus-1
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IU	International unit
kg	Kilogram
mIU	milli-international units
mg	Milligram
MI	Maturation inhibitor
mL	millilitre
msec	Millisecond
ng	Nanogram
NIMP	Non-investigational medicinal product
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using the Fridericia formula
SAD	Single ascending dose
SAE	Serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of activities
SRM	Study Reference Manual
SCN5A	Sodium Voltage-Gated Channel Alpha Subunit 5
t1/2	Apparent terminal phase half-life
tlag	Lag time for absorption
Tmax	Time of maximum observed concentration

TQT	Thorough QT
ULN	Upper limit of normal
VH	ViiV Healthcare
Vz/F	Apparent volume of distribution
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of ViiV Healthcare
Portia
Tivicay

Trademarks not owned by ViiV Healthcare
DAIDS
SAS
WinNonlin

11. REFERENCES

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

Buzzi M, Wandeler G, Anderegg N et al. Dolutegravir-based maintenance therapy in HIV-infected patients: systematic review and meta-analysis. 16 European AIDS Conference - European AIDS Clinical Society (EACS). 2017; Accessed at: http://natap.org/2017/EACS/EACS_41.htm

Clotet B, Feinberg J, Van Lunzen J, et al. Once−daily dolutegravir versus darunavir plus ritonavir in antiretroviral−naïve adults with HIV−1 infection (FLAMINGO): 48 week results from the randomised open−label phase 3b study. Lancet. 2014;383:2222−2231.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Drug Evaluation and Research (US). Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies. December 2002. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/food-effect-bioavailability-and-fed-bioequivalence-studies.

Department of Health and Human Services (DHHS), National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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

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

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

GSK Document Number 2018N379610_02. Clinical Investigator's Brochure for GSK3640254, November 2020

GSK Document Number RM2007/00683/14. Clinical Investigator's Brochure for GSK1349572, September 2020

GSK Document Number 2019N399207_03. Clinical Protocol 208379, Phase IIb, randomized, partially blind, active controlled, dose-range finding study of GSK3640254 compared to a reference arm of dolutegravir, each in combination with nucleoside reverse transcriptase inhibitors, in HIV-1 infected antiretroviral treatment-naive adults 25-SEP-2020

GSK Document Number 2019N399318_00. Clinical Protocol 209712, An Open Label Two-way Interaction Clinical Trial to Evaluate the Pharmacokinetic Interactions Between GSK3640254 and Dolutegravir in Healthy Subjects 12-DEC-2018

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

GSK Document Number 2010N105142_00. Clinical Protocol ING113674, Relative bioavailability study of three different tablet formulations of GSK1349572 50 mg and the Dose Proportionality of and Effect of Food on the Selected Formulation in healthy male and female volunteers

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

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37:1779-84.

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

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

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

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

Raffi F, Jaeger H, Quiros-Roldan E, et al.; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, noninferiority trial. Lancet Infect Dis. 2013;13(11):927-935.

Rome Foundation. Rome IV Diagnostic Criteria for Functional Gastrointestinal Disorders. 2019. Available from: https://romeonline.org/?product=rome-iv-diagnostic-algorithms-for-common-gi-symptoms-second-edition. Accessed 19 January 2021.

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

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

Tivicay Prescribing Information. ViiV Healthcare, June 2020. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL-IFU.PDF. Accessed 19 January 2021.

Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369(19):1807-1818.

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