PROTOCOL

Study ID: 212483

Official Title of Study A Phase IIb, randomized, double-blind, parallel-group study to assess the efficacy, safety, tolerability, and resistance profile of GSK3640254 in combination with dolutegravir compared to dolutegravir plus lamivudine in HIV-1 infected, treatmentnaïve adults

NCT ID-NCT04900038

Approval Date of Document: 11-Aug-2022

TITLE PAGE

Protocol Title: A Phase IIb, randomized, double-blind, parallel-group study to assess the efficacy, safety, tolerability, and resistance profile of GSK3640254 in combination with dolutegravir compared to dolutegravir plus lamivudine in HIV-1 infected, treatment-naïve adults

Protocol Number: 212483/Amendment 03

Compound Number or Name: GSK3640254

Brief Title: A Phase IIb Clinical Trial of GSK3640254 + Dolutegravir (DTG) in HIV-1 Infected Treatment-Naive Adults

Study Phase: Phase 2b

Acronym: DYNAMIC

Sponsor Name and Legal Registered Address (excluding US):

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

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 1 919 438 2100
In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Senior Vice President, Head of Research & Development.

This study is sponsored by ViiV Healthcare. GlaxoSmithKline and Syneos Health are supporting ViiV Healthcare in the conduct of this study.

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

PPD

ViiV Healthcare Research & Development

Approval Date: 11 Aug 2022

Regulatory Agency Identifying Number(s):

IND: 139838

EudraCT: 2021-000016-28

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 03	*11 Aug 2022*	TMF-14435461
Amendment 02	*02-SEP-2021*	TMF-12456180
Amendment 01	*19-MAR-2021*	TMF-11880342
Original Protocol	*11-FEB-2021*	TMF-2196391

Amendment 03: 11 Aug 2022

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Study 212483 has always included an option for participants to have continued access to study treatment after they complete the study, provided they meet certain criteria. As the study is approaching the end of enrolment, this amendment has been prepared to provide detail of the visits and assessments that a participant would be expected to complete if they are granted continued access to study treatment. Clarification has also been added for the timing at a participant level of transition from non-optimal GSK3640254 dose to optimal dose in the double-blind phase of the study and from blinded to unblinded study treatment. Specifically, this amendment clarifies that participants may not have all transitions, depending on their entry date into the study and the timing of the interim analyses required for those transitions to occur.

Additional minor clarifications and corrections have been made throughout.

Section # and Name	Description of Change	Brief Rationale
Title Page	ViiV Healthcare copyright statement added	Requirement of new protocol template
1.2 Schema	Schema Figure and footnotes were updated as follows: • Clarified that participants who reach their Week 24 visit before the optimal dose of GSK3640254 is known will remain on their original GSK3640254 dose	Clarity on timing of transition from original dose of GSK3640254 to optimal dose and about when an individual participant's treatment allocation would be unblinded.

Section # and Name	Description of Change	Brief Rationale
	until the optimal dose is known (expected prior to the overall study's Week 24 primary endpoint). Treatment allocation will remain blinded until after the Week 24 primary endpoint analysis, then will become open label. • Clarified the treatment options for participants who meet the criteria for continued access to study treatment beyond the end of the study, depending on when they reach their Week 52 visit compared to the treatment transition milestones of the study. Participants on GSK3640254 arms may continue to receive study medication beyond their individual Week 52 visit. Based on the above sequence of events and when each participant reaches Week 52 relative to the Week 24 primary endpoint analysis, participants on GSK3640254 arms may receive: double blind non-optimal dose, double blind optimal dose, and/or open label optimal dose. Participants on the reference arm may continue to receive	Treatment options for continued access were not previously described and have been added.

Section # and Name	Description of Change	Brief Rationale
	DTG + 3TC only if they reach their individual Week 52 visit during the Blind Treatment Phase. After the Open Treatment Phase starts, DTG + 3TC will be discontinued for all participants who have completed Week 52.	
1.1 Synopsis 4.1 Overall Design	Clarified that the transition from the double-blind phase to open-label phase is linked to the timing of the last participant's week 24 visit.	Change made to address confusion about when each participant's treatment allocation would be unblinded. All treatment allocations will remain blinded until after the primary endpoint analysis, which will occur after all participants have completed their Week 24 visit.
1.1 Synopsis 4.1.4 Study Completion 6.6 Continued Access to Study Intervention after the End of the Study	Expanded existing text regarding continued access to study treatment at the end of the study, to cover the options for participants who reach their Week 52 visit before an optimal dose of GSK3640254 is determined and/or before the study enters the open-label phase. Deleted duplicated paragraph in the synopsis.	The protocol was initially written assuming that recruitment into the study would be such that participants would all reach individual key milestones during the same phase of the study i.e. transition to GSK3640254 optimal dose would occur before any participant reached their Week 24 visit and transition to the Open-label Phase would occur before any participant completed the study. Due to slower than anticipated recruitment this is not the case and the potential treatment allocations and transitions required for a participant who meets the criteria for continued access have been added.
1.3 Schedule of Activities (SoA)	Visit schedule and assessments have been added for participants who meet the criteria for and consent to continued access to study	No visit schedule or list of planned assessments had previously been included. Original wording of footnote 20 was unclear and potentially gave

Section # and Name	Description of Change	Brief Rationale
	treatment. Footnote 5 has been updated to add the separate consent required for continued access beyond the end of the study. Footnote 4 has been updated to clarify that, if a participant is unable to attend a visit during the protocol-defined window, sites should discuss measures to ensure continued access to study treatment and assessments with the Sponsor. Clarification to footnote 20 to state that urine pregnancy testing every 4 weeks at home is required only if virtual visits occur. Added footnote 23 to state requirement for dispensing visits every 4 weeks for participants who are granted continued access to study treatment while the study is in the Double-Blind Treatment Phase.	the impression that both serum and urine pregnancy tests were required. Participants who meet the criteria for pregnancy testing are required to have a serum pregnancy test at each on site visit. Urine pregnancy tests are only required if virtual visits occur and the participant needs to perform the test at home. The protocol previously only included measures to follow to ensure continued access to study treatment and study assessments if a visit was missed or delayed due to COVID-19. No instructions were given for steps to take if a participant had to miss or delay a visit due to unforeseen circumstances and have now been added. Dispensing visits and requirements for continued access were not previously described and have been added.
1.1 Synopsis 4.1 Overall Design 4.1.4 Study Completion	Updates to reflect the fact that the initial IDMC review in study 208379 has occurred and a no-action letter was issued for study 208379 with no change subsequently required in this study 212483. Details of the potential outcomes from the initial IDMC meeting in study 208379 and their impact on study 212483 were deleted.	Updated to reflect the outcome of the initial IDMC review in study 208379.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Clarified the contents of the 5 bottles of study treatment given to participants at each visit and the number of Tablets/capsules taken by participants during the Double-blind and Open-label phases of the study. Added that participants will be issued a spare bottle of DTG at Day 1 only, that they will keep for the whole study to provide overage in case of delayed study visits.	Clarification added to address recurring queries from EC/CAs and sites. DTG bottles only contain 30 Tablets and visits are scheduled every 4 weeks (28 days). The additional, spare bottle is intended to cover unavoidable delays in study visits where a participant would otherwise run out of DTG.
7.2 Participant Discontinuation/Withdrawal from the Study	Added that an early discontinuation/withdrawal visit should also be conducted if a participant who has been entered into the Continued Access Phase discontinues or is withdrawn from study treatment.	Requirements for continued access were not previously described and have been added.

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY 12
1.1. Synopsis 12
1.2. Schema 16
1.3. Schedule of Activities (SoA) 17

2. INTRODUCTION 21
2.1. Study Rationale 24
2.2. Background 24
2.2.1. Key Safety Data with a Prior Maturation Inhibitor (GSK3532795) 24
2.2.2. Preclinical Summary with GSK3640254 24
2.2.3. Key Clinical Data on GSK3640254 to date 26
2.2.4. Key Phase 2a (Study 208132) Clinical Data on GSK3640254 27
2.3. Benefit/Risk Assessment 31
2.3.1. Risk Assessment 33
2.3.2. Benefit Assessment 43
2.3.3. Overall Benefit: Risk Conclusion 43

3. OBJECTIVES AND ENDPOINTS 43

4. STUDY DESIGN 45
4.1. Overall Design 45
4.1.1. Screening Period 48
4.1.2. Treatment Period 48
4.1.3. Follow-up 50
4.1.4. Study Completion 50
4.2. Scientific Rationale for Study Design 51
4.2.1. Participant Input into Design 52
4.3. Justification for Dose 52
4.4. End of Study Definition 57

5. STUDY POPULATION 57
5.1. Inclusion Criteria 58
5.2. Exclusion Criteria 59
5.3. Lifestyle Considerations 64
5.3.1. Meals and Dietary Restrictions 64
5.3.2. Caffeine, Alcohol, and Tobacco 64
5.3.3. Activity 64
5.3.4. Counsel regarding safe sex practices 64
5.4. Screen Failures 64

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 65
6.1. Study Intervention(s) Administered 66
6.2. Preparation/Handling/Storage/Accountability 66
6.3. Measures to Minimize Bias: Randomization and Blinding 67
6.4. Study Intervention Compliance 68
6.5. Dose Modification 68
6.6. Continued Access to Study Intervention after the End of the Study 68

6.7. Treatment of Overdose 69
6.8. Concomitant Therapy 70
6.8.1. Prohibited Medications and Non-Drug Therapies 71

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 73
7.1. Discontinuation of Study Intervention 73
7.1.1. Protocol-Defined Virologic Failure 74
7.1.2. Liver Chemistry Stopping Criteria 78
7.1.3. Columbia-Suicide Severity Rating Scale 79
7.1.4. QTc Stopping Criteria 79
7.1.5. Temporary Discontinuation 79
7.2. Participant Discontinuation/Withdrawal from the Study 80
7.3. Lost to Follow Up 80

8. STUDY ASSESSMENTS AND PROCEDURES 81
8.1. Efficacy Assessments 81
8.1.1. Lymphocyte Subsets by Flow Cytometry 81
8.1.2. Disease Progression 82
8.2. Safety Assessments 82
8.2.1. Physical Examinations 82
8.2.2. Vital Signs 83
8.2.3. Cardiac Monitoring with Electrocardiograms 84
8.2.4. Clinical Safety Laboratory Assessments 84
8.2.5. Pregnancy Testing 85
8.2.6. Suicidal Ideation and Behaviour Risk Monitoring 85
8.2.7. GI Intolerability Evaluation & Monitoring Plan (with Stopping Criteria) 87
8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting 90
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 91
8.3.2. Method of Detecting AEs and SAEs 91
8.3.3. Follow-up of AEs and SAEs 91
8.3.4. Regulatory Reporting Requirements for SAEs 92
8.3.5. Pregnancy 92
8.3.6. Cardiovascular and Death Events 93
8.3.7. Disease-Related Events and/or Disease-Related Outcomes (HIV-Associated Conditions) 93
8.3.8. Adverse Events of Special Interest 94
8.4. Pharmacokinetics 94
8.5. Genetics and/or Pharmacogenomics 96
8.6. Biomarkers 96
8.6.1. Viral Genotyping and Phenotyping Analyses 96
8.7. Immunogenicity Assessments 97
8.8. Medical Resource Utilization and Health Economics 97

9. STATISTICAL CONSIDERATIONS 98
9.1. Statistical Hypotheses 98
9.2. Sample Size Determination 98
9.2.1. Sample Size Sensitivity 99
9.3. Analysis Sets 100

9.3.1. Intent-to-Treat Exposed Population (ITT-E) 100
9.3.2. Per Protocol Population (PP) 101
9.3.3. Pharmacokinetic Population 101
9.3.4. Safety Population 101
9.4. Statistical Analyses 101
9.4.1. Efficacy Analysis 101
9.4.2. Safety Analysis 102
CCI [redacted]
9.5. Other Analysis 103
9.6. Interim Analysis 103
9.6.1. Independent Data Monitoring Committee 104

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 105
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 105
10.1.1. Regulatory and Ethical Considerations 105
10.1.2. Financial Disclosure 105
10.1.3. Informed Consent Process 106
10.1.4. Data Protection 106
10.1.5. Committees Structure 107
10.1.6. Dissemination of Clinical Study Data 107
10.1.7. Data Quality Assurance 108
10.1.8. Source Documents 109
10.1.9. Study and Site Start and Closure 109
10.1.10. Publication Policy 110
10.2. Appendix 2: Clinical Laboratory Tests 111
10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 113
10.3.1. Definition of AE 113
10.3.2. Definition of SAE 114
10.3.3. Definition of Cardiovascular Events 115
10.3.4. Recording and Follow-Up of AE and SAE 116
10.3.5. Reporting of SAE to GSK/ViiV Healthcare/Syneos Health 118
10.4. Appendix 4: Contraceptive and Barrier Guidance 119
10.4.1. Definitions: 119
10.4.2. Contraception Guidance: 119
10.5. Appendix 5: Genetics 122
10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments 123
10.7. Appendix 7: Child-Pugh Classification 127
10.8. Appendix 8: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017 128
10.9. Appendix 9: Toxicity Management 129
10.9.1. Liver Chemistry Stopping and Follow-up Criteria 130
10.9.2. Hypersensitivity Reaction 130
10.9.3. Rash & Skin Reactions 131
10.9.4. Hypertriglyceridemia/Hypercholesterolemia 132
10.9.5. Creatine Phosphokinase (CPK) Elevation 132
10.9.6. Decline in Renal Function 132
10.9.7. Proximal Renal Tube Dysfunction 133

10.9.8. Proteinuria 133
10.10. Appendix 10: CDC Classification for HIV-1 Infection (2014) 134
10.11. Appendix 11: COVID-19 Pandemic and Clinical Trial Continuity 136
10.11.1. Changes to Study Visits and Study Procedures 136
10.11.2. Changes to Informed Consent 138
10.11.3. Direct-To-Patient (DTP) Shipment of Study IP 138
10.11.4. COVID-19 Therapeutic Agents 139
10.11.5. COVID-19 Specific Data Capture 139
10.12. Appendix 12: Abbreviations and Trademarks 142
10.13. Appendix 13: Protocol Amendment History 147

11. REFERENCES 156

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase IIb, randomized, double-blind, parallel-group study to assess the efficacy, safety, tolerability, and resistance profile of GSK3640254 in combination with dolutegravir compared to dolutegravir plus lamivudine in HIV-1 infected, treatment-naïve adults

Brief Title: A Phase IIb Clinical Trial of GSK3640254 + Dolutegravir (DTG) in HIV-1 Infected Treatment-Naive Adults

Rationale:

The Sponsor proposes conducting this Phase 2b study, the primary objective of which is to evaluate the efficacy of GSK3640254 (initially, at three doses: 100, 150, and 200 mg) + DTG relative to DTG + 3TC by analyzing the proportion of Virologic Responders (HIV-1 RNA <50 c/mL at Week 24). Secondary objectives are to evaluate: 1) longer term efficacy at Week 48, 2) safety/tolerability, and 3) cumulative resistance. The totality of this data (from a planned interim analysis onwards) would inform the basis of subsequent Phase 3 clinical trials in treatment experienced participants living with HIV-1; specifically two Phase 3 clinical trials will evaluate the clinical profile of GSK3640254 + DTG in HIV-1 infected participants). Although the Phase 3 dose selection will be based on another parallel Phase 2b trial, Study 208379 (GSK3640254 100, 150 or 200 mg +2 NRTIs in HIV-1 infected treatment naïve adults), available data from this study may be integrated into that decision if available/appropriate.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate antiviral efficacy of GSK3640254 + DTG, relative to DTG + 3TC at Week 24 in HIV-1-infected, ART-naïve participants	• Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 using the FDA snapshot algorithm
Secondary	
• To evaluate the antiviral activity of GSK3640254 + DTG relative to DTG + 3TC at Week 48	• Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm • Absolute values and changes from baseline in HIV-1 RNA through Weeks 24 and 48

Objectives	Endpoints
	• Absolute values and changes from baseline in CD4+ T-cell counts through Weeks 24 and 48
• To evaluate safety and tolerability of GSK3640254 when given in combination with DTG, relative to DTG + 3TC	• Frequency of SAEs, Deaths and AEs leading to Discontinuation through Weeks 24 and 48 • AEs of special interest (AESIs) through Weeks 24 and 48
• To assess the development of viral resistance to GSK3640254 and other on-study ART in participants experiencing virologic failure through Week 48	• Changes in genotypic and/or phenotypic profiles of virus compared to baseline
• To assess the steady-state exposure of GSK3640254 when given in combination with DTG	• The steady-state plasma PK parameters of GSK3640254 will be assessed based on Sparse PK sampling through Week 48

Overall Design:

Study 212483 is a Phase IIb, randomized, multicentre, double-blind, active-controlled, parallel group study to be conducted in approximately 80 ART-naïve adults living with HIV-1. Participants will be stratified by screening plasma HIV-1 RNA, by <100,000 c/mL or ≥100,000 c/mL, and randomized to one of the three doses of blinded GSK3640254 (100, 150, or 200 mg) or a reference arm of blinded 3TC – each in combination with open label DTG. The study will include a Screening Phase (to a maximum of 30 days), a double-blind Randomized Phase (first participant Day 1 to last participant Week 24) and an open-label Randomized Phase (last participant Week 24 to all ongoing participant's Week 52). The study will be double-blind through completion of the overall study's Week 24 primary endpoint analysis (achieved at least after the last participant completes their Week 24 visit).

There may be modifications to study arm recruitment and/or study arm continuation and/or design in 212483 based on the outcome of: 1) a 212483 IDMC review prior to the Week 24 primary endpoint or 2) the results of an ongoing Phase 2b trial in HIV-1 infected treatment naïve adults (Study 208379): the 208379 Week 24 primary endpoint (selection of an optimal dose from either 100, 150, or 200 mg). Further details on the implications of the analyses from these two parallel Phase 2 studies on the experimental dosing arms of study 212483 are described in the protocol.

Brief Summary:

Approximately 80 treatment-naïve, adult participants living with HIV-1 will be randomized into this Phase 2b study, the primary objective of which is to evaluate the

efficacy of GSK3640254 (initially, at three doses: 100, 150 and 200 mg) + DTG relative to DTG + 3TC by analyzing the proportion of Virologic Responders (participants with HIV-1 RNA <50 c/mL at Week 24). Participants will be stratified by screening plasma HIV-1 RNA, by <100,000 c/mL or ≥100,000 c/mL, and will participate for at least 52 weeks. Participants will be followed at visits approximately every 4 weeks.

Number of Participants:

Approximately 160 participants will be screened to achieve approximately 80 randomly assigned to one of 4 arms of the study interventions, approximately 20 per GSK3640254 arm, and approximately 20 in the DTG + 3TC Reference Arm. Targets to increase diversity will be defined at a country level in the study recruitment plans.

Intervention Groups and Duration:

The study will include:

- A Screening Phase to a maximum of 30 days
- A Double-blind Randomized Phase (first participant Day 1 to last participant Week 24)
- An Open-label Randomized Phase (at least last participant Week 24 to last participant Week 52)

At Day 1, participants will be randomized to receive:

- Arm 1: Blinded GSK3640254 100 mg + Unblinded DTG 50 mg
- Arm 2: Blinded GSK3640254 150 mg + Unblinded DTG 50 mg
- Arm 3: Blinded GSK3640254 200 mg + Unblinded DTG 50 mg
- Arm 4: Unblinded DTG 50 mg + Blinded 3TC 300 mg

- To provide continued access to an investigational drug to participants deriving therapeutic benefit, participants who have successfully completed 52 weeks of treatment may be given the opportunity to continue to receive their study treatment. During the blinded randomized phase: that could be non-optimal GSK3640254 + DTG, optimal GSK3640254 + DTG, or 3TC + DTG).
- During the open label randomized phase:
    - Any participant who received 3TC + DTG beyond their individual Week 52 visit will discontinue from the study and be transferred to locally available standard of care treatment.
    - Any participant who received GSK3640254 + DTG beyond their individual Week 52 visit will be switched to a single optimal dose of GSK3640254 once it is determined from the ongoing Study 208379. After this occurs, participants who continue to receive GSK3640254 + DTG beyond their individualized Week 52 will have the option to continue on open label optimal dose GSK3640254 + DTG until either they or their healthcare provider decide to discontinue study treatment or until

GSK3640254 + DTG is receives local marketing authorization and is commercially available).

- Continued access to GSK3640254 + DTG in Study 212483 may occur, as described above, provided all of the following conditions are met:
  - There is evidence of continued clinical benefit for the participant, and
  - There are no comparable alternative treatment options available, and
  - Such provision of GSK3640254 + DTG is permitted under local laws and regulations.

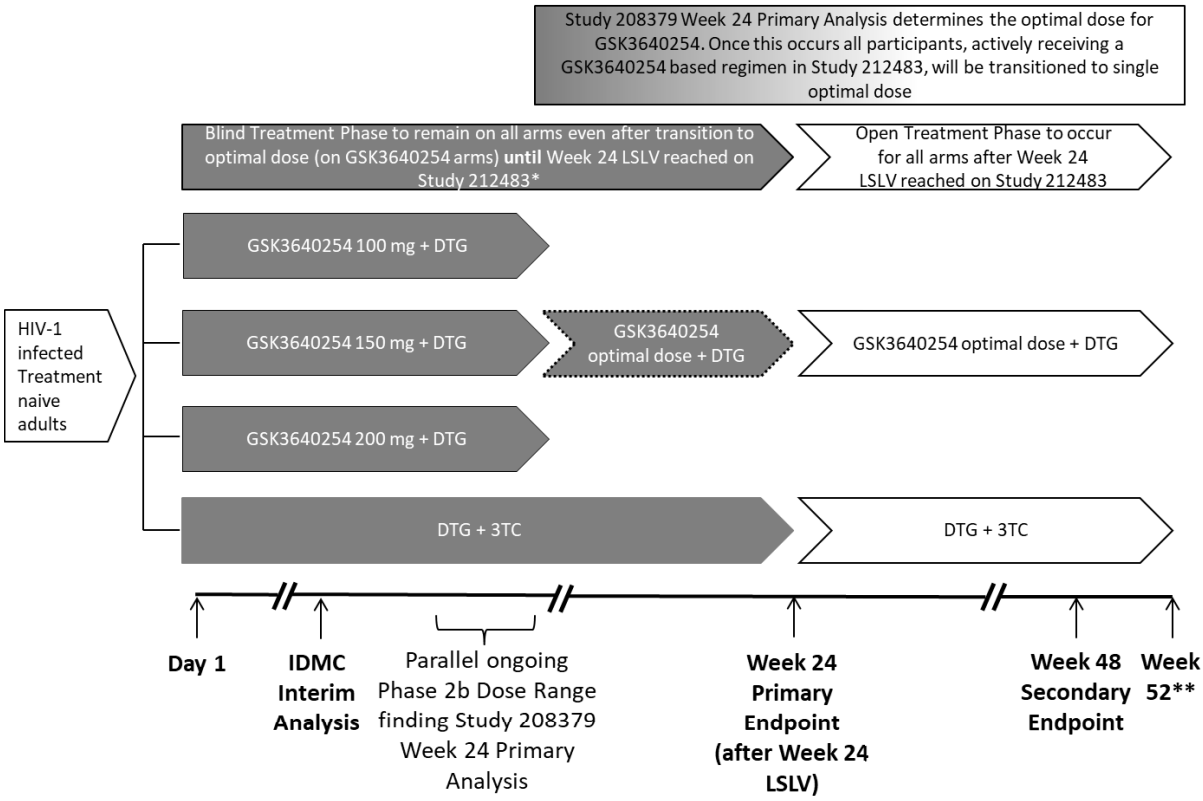
Continued access to an investigational drug will cease if the participant no longer derives clinical benefit from receipt of GSK3640254 + DTG; the participant meets a protocol-defined reason for discontinuation; or the development of GSK3640254 + DTG is discontinued.

Independent Data Monitoring Committee (IDMC):

This study will utilize an Independent Data Monitoring Committee (IDMC) to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of participants and to protect the scientific validity of the study. An ad-hoc review of data by the IDMC will be triggered when the number of participants exceeds thresholds pre-specified in the IDMC charter for either: protocol-defined virologic failure criteria or number of safety/tolerability events. In addition, the IDMC will be triggered at least at one timepoint prior to the Week 24 primary endpoint (independent of an event-based trigger). Full details of the methods,

timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

1.2. Schema



*Participants in this study (212483) reaching Week 24 before selection of the GSK3640254 optimal dose in Study 208379 will continue on their original GSK3640254 dose until the optimal dose is known (expected prior to the overall study's Week 24 primary endpoint). Treatment allocation will remain blinded until after the Week 24 primary endpoint analysis, then will become open label.

**Participants on GSK3640254 arms may continue to receive study medication beyond their individual Week 52 visit. Based on the above sequence of events and when each participant reaches Week 52 relative to the Week 24 primary endpoint analysis, participants on GSK3640254 arms may receive: double blind non-optimal dose, double blind optimal dose, and/or open label optimal dose. Participants on the reference arm may continue to receive DTG + 3TC only if they reach their individual Week 52 visit during the Blind Treatment Phase. After the Open Treatment Phase starts, DTG + 3TC will be discontinued for all participants who have completed Week 52. Please see protocol Section 6.6 for full details.

1.3. Schedule of Activities (SoA)

Procedures[1]	Screening (up to 30 days before Day 1)	Intervention Period[2]														Continued access phase[4]	Early Discontinuation/withdrawal	Follow- up[5]
			Week															
		Day 1 (Baseline)	2	4	8	12	16	20	24	28	32	36	40	44	48	52[3]	Every 12 weeks after Week 52	
Clinical and Other Assessments																		
Informed consent[6]	X														X			
Inclusion and exclusion criteria	X	X																
Demography	X																	
Prior ARV history to ensure naïve status	X																	
Medical history[7]	X																	
Height, weight (W) and BMI[8]	X	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Physical exam (F=Full, T=Targeted)[10]		F					T		T						T		T		
CDC HIV-1 Classification[11]	X	X																
HIV-associated conditions[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale (C-SSRS)[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adherence review[14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event (AE)/SAE assessments	SAE Only	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG: single reading[15]	X																	X	
ECG: single reading PRE-dose[15]			X																
ECG: triplicate readings PRE-dose to establish baseline average QTcF[15]		X																	

Procedures[1]	**Screening (up to 30 days before Day 1)**	**Intervention Period**[2]															**Continued access phase**[4]	**Early Discontinuation/withdrawal**	**Follow- up**[5]
		Day 1 (Baseline)	**Week**																
			2	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**[3]	**Every 12 weeks after Week 52**		
ECG: single readings POST-dose at 2, 4 and 6 hours[15]		X	X[16]																
ECG: single reading POST-dose any time between 2-6 hrs[15]						X			X						X				
Laboratory Assessments																			
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
T-cell Lymphocyte subset	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma for storage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma for Geno/Phenotypic Resistance Assays[17]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Clinical chemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PT/INR (For Child-Pugh)	X																		
Fasting lipids and glucose[18]	X	X				X			X						X			X	
Urine Drugs of Abuse panel[19]	X																		
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pregnancy test for POCBP only[20]	S	U/S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, Anti-HBs, and reflex HBV DNA	X																		
HCV antibody and reflex HCV RNA	X																		
Rapid Plasma Reagin (RPR)	X																		
Pharmacokinetics – Sparse[21]			X	X	X	X			X						X				

Procedures[1]	Screening (up to 30 days before Day 1)	Intervention Period[2]															Continued access phase[4]	Early Discontinuation/withdrawal	Follow- up[5]
			Week																
		Day 1 (Baseline)	2	4	8	12	16	20	24	28	32	36	40	44	48	52[3]	Every 12 weeks after Week 52		
Optional Genetics sample[22]		X																	
Study Treatment																			
Randomization		X																	
IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X	X
Dispense IP		X		X	X	X	X	X	X	X	X	X	X	X	X		X[23]		
IP accountability (pill counts)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X	

Abbreviations: BMI: Body mass index; CDC: Center for Disease Control and Prevention; HIV: Human immunodeficiency virus; ECG: Electrocardiogram; RNA: Ribonucleic Acid; POCBP: Participant of Childbearing Potential; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C Virus; IVRS/IWRS: Interactive Voice/Web Response System

1. Order of Assessments (pre-dose): C-SSRS – ECG – Vital Signs – Blood Draws (see notes in Section 8.4 regarding order for blood draw and ECG during the Week 2 visit)
2. The acceptable window around any visit, Week 4 and beyond, is ± 2 days. Participant must come in no later than +2 days of the visit windows or participant will run out of drug supply. If, due to unforeseen circumstances, a participant is unable to attend a visit during the visit window, measures for ensuring continued antiretroviral treatment and safety monitoring of the participant (e.g., those described in Section 10.11 for missed visits due to COVID-19), should be discussed and agreed with the Sponsor before implementation.
3. Participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, occurring prior to Week 52.
4. Participants who meet the criteria to be offered continued access to study treatment after Week 52 (see Section 6.6) will take part in the Continued Access Phase. Any participant who discontinues study treatment while in the Continued Access Phase for any reason, will attend withdrawal and follow-up visits.
5. See Section 4.1.3.
6. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility including review of additional assessments performed at Day 1. Consent for the continued access phase of the study must be obtained from the patient before or at their Week 48 visit, to allow additional medication to be allocated and dispensed at their Week 52 visit.

7. Medical History includes substance usage and the Medical Conditions listed in Exclusion Criteria in Section 5.2, as well as assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), and, in particular, but not limited to, cardiac, psychiatric, renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders including current medical conditions.
8. See Section 8.2.1.1.
9. See Section 8.2.2.
10. See Section 8.2.1.
11. See Section 10.10.
12. The Concomitant Medication review at Screening includes those listed in Section 6.8 to be considered relative to dosing requirements.
13. On Day 1, participants will provide response to the eC-SSRS Baseline form ***prior to*** the RAMOS task of Randomization. The eC-SSRS will be in electronic format, responses provided by participants either by phone or computer, whether they are in clinic or if they are remote (virtual visits). Participants can complete the eC-SSRS ±7 days from each visit post-randomization. See Section 8.2.6.
14. Adherence review includes pill count, review of any recorded missed doses, and a conversation about other possible missed doses if the pill count does not match those recorded and/or verbally reported.
15. See Section 8.2.3 for details. Window for ECGs is ± 15 minutes.
16. If there are COVID-19 impacts that restrict the ability for a participant to come to the clinic for the day-long visit at Week 2, then, at the least, all participants should attend the clinic visit for the collection of HIV-1 RNA and as many of the ECGs as possible.
17. See Section 7.1.1. Unused plasma samples collected for the potential need of resistance testing will enter long-term storage and are then included in the pool of samples that can be used for further research, if participant has consented.
18. An overnight fast is preferred prior to visits that include lipid assessments, but a minimum of 6 hours is acceptable.
19. Also to be done for any Grade 3-4 Psychiatric AE. See Section 8.2.6.
20. At Screening, and for POCBP only, sites will submit serum for FSH and Estradiol, and for Pregnancy testing. On Day 1, in addition to the serum sample sent to the central lab, a urine pregnancy test will be done in the clinic to confirm negative status prior to IP administration. If the urine test result is ambiguous, the site should await the results of the Day 1 serum test before study treatment can be initiated. On Treatment, a blood sample will be collected at each visit for serum pregnancy testing. Urine pregnancy tests will be done every 4 weeks at home, only if virtual visits occur (results need to be reported to the site). Any ambiguous urine result will need to be retested in serum. S=serum, U=urine
21. See Section 8.4 for details.
22. A separate genetics ICF is required.
23. If a participant is granted continued access to study treatment while the study is still in the Double-blind Treatment Phase, they will be required to return every 4 weeks to collect new study treatment. No other procedures or assessments will be performed at those dispensing visits.

2. INTRODUCTION

Infection with Human immunodeficiency virus-1 (HIV-1) continues to be a serious health threat throughout the world, with more than 40 million individuals living with HIV worldwide. The current standard of care treatment for HIV-1 is combination anti-retroviral therapy (cART) with recommendations to start regardless of CD4+ T-cell count, committing people living with HIV to lifelong, life-saving therapy (European AIDS Clinical Society (EACS) Guidelines, 2020). However, the chronic exposure to cART has identified anti-retroviral (ARV)-associated long-term toxicities (e.g. central nervous system (CNS) or cardiovascular (CV)/metabolic effects, renal disease, etc.), creating a need to address and prevent these co-morbidities. Also, treatment failure remains a continuing concern in clinical care due to the presence and emergence of resistant strains and tolerability issues. The aging population of people living with HIV drives a need for drugs with fewer drug-drug interactions. In this environment, medicines with novel mechanisms of action (MoA) that can be used as part of a preferred cART regimen have an important role to play. However, to be successful, a new ARV agent must be safe and effective, provide a relatively high barrier to resistance, have low toxicity, have minimal drug-drug interactions, and preferably be a relatively low-dose once-a-day drug that can be combined with other agents as part of a fixed-dose regimen. GSK3640254, a next generation HIV-1 maturation inhibitor (MI), has the potential to meet such valued features for a new ARV medicine.

Rationale for 2 Drug Regimen

Fixed-dose combination therapy as a single Tablet regimen (STR) is preferred by many patients and has well-recognized benefits. These include the simplification of therapy by combining two products in fixed proportions into a single Tablet with the potential to increase patient adherence due to it being a simpler regimen. This also avoids the risk of "partial adherence", where patients take some, but not all, of their medicines. Better compliance with full treatment regimens can decrease the likelihood of virologic failure and subsequent development of resistance. While some STR options are now available, the opportunity to develop new STRs to better address toxicities and simplify treatment regimens for treatment-experienced patients while concurrently suppressing the emergence of resistance remains.

Current treatment guidelines recommend the use of 2-3 drugs to construct a complete regimen for the treatment of HIV-1 in treatment naïve adults: 1) an integrase inhibitor based regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) or 2) dolutegravir (DTG)/lamivudine (3TC), except for individuals with HIV ribonucleic acid (RNA) >500,000 c/mL or HBV coinfection [Panel on Antiretroviral Guidelines for Adults and Adolescents, 2021; European AIDS Clinical Society (EACS) Guidelines, 2020]. There continues to be an interest in the use of 2-drug regimens due to the potential of reduced drug-related toxicities and preserving future treatment options.

Rationale for Dolutegravir

Dolutegravir is a potent dual cation binding INSTI, exhibiting rapid reduction in viral load, best in class 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, pharmacokinetics (PK), safety and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to IIIB clinical trials [GlaxoSmithKline Document Number RM2007/00683/14].

Dolutegravir in combination with other antiretroviral(s) has been shown to be beneficial to treatment naïve and treatment experienced patients (with or without prior Integrase resistance associated mutations). Given the Sponsor's Phase 3 clinical plans to evaluate a fixed dose combination (FDC) of GSK3640254/DTG in HIV-1 infected virologically suppressed treatment experienced adults, the efficacy and resistance profiles of contemporary two-drug regimens containing DTG are summarized here: either as maintenance of suppression or induction of therapy.

ViiV Healthcare's SWORD-1 and -2 studies (DTG + Rilpivirine; switch indication in suppressed patients without prior failure or known resistance) showed non-inferiority in the maintenance of virologic suppression over 48 weeks following a switch to dolutegravir-rilpivirine compared with continuing current ARV regimen in both the individual studies and in the pooled SWORD data analysis [Llibre, 2018]. At Week 100 in the Early Switch group, 456 (89%) had VL <50 c/mL. One participant with RPV resistance at confirmed virologic withdrawal (Early Switch group, Week 100) had pre-existing non-nucleoside reverse transcriptase inhibitors (NNRTI) mutations at baseline. No participants developed INSTI resistance [Aboud, 2019].

ViiV Healthcare's GEMINI-1 and -2 studies showed non-inferior efficacy and similar tolerability profiles of dolutegravir plus lamivudine to a guideline-recommended three-drug regimen at 48 weeks in ART-naive adults and supports its use as initial therapy for patients with HIV-1 infection [Cahn, 2019]. The 2-drug regimen, dolutegravir/lamivudine (DTG/3TC) FDC, has a robust antiviral activity, safety profile, high barrier to resistance, low potential for DDIs, and can be administered as a once-daily single Tablet regimen (STR) through Week 96 [Cahn, 2019].

ViiV Healthcare's TANGO study (dolutegravir plus lamivudine switch in suppressed patients for > 6 months without prior failure or known NRTI or INI major resistance mutations) remains ongoing. Data through Week 96 showed the combination of DTG and 3TC is non-inferior to continuing a TAF based three-drug regimen [Van Wyk, 2020]. These five studies show DTG plus an additional ARV agent is an effective treatment option for adults living with HIV-1.

Finally, beyond the five clinical trials summarized above, DTG-based regimens have demonstrated robust clinical outcomes in other Phase III studies. Further, DTG has been shown to be potent and to have a high barrier to resistance, and in clinical studies of treatment-naïve participants, DTG-based regimens have not been associated with the development of resistance to any component, demonstrating the clinical benefit of DTG-based regimens in this population.

Rationale for Maturation Inhibitor (MI)

GSK3640254 is a next-generation HIV-1 MI which binds near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton (kDa) HIV capsid (CA) protein p24 (CA [p24]) and spacer peptide 1 (SP1). Blockage at this step results in the release of immature non-infectious virus particles. Other small molecules within this class have demonstrated a Pharmacokinetic (PK)/Pharmacodynamic (PD) relationship and longer-term efficacy through Phase 2a-2b trials.

As of February 2021, GSK3640254 has completed a Phase 2a study (short-term, monotherapy, proof of concept [POC]). Additionally, the safety, tolerability, and PK have been evaluated in eight other completed Phase 1 studies in healthy volunteers. The totality of the clinical data shows: 1) GSK3640254 is generally well-tolerated in short-term studies, and 2) GSK3640254 has a short-term PK/PD (decline in HIV-1 RNA) relationship. Summaries of the pre-clinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number 2018N379610_02]. A multinational dose range finding study (Study 208379) is ongoing utilizing the same three doses of GSK3640254 as this proposed study (100, 150, and 200 mg).

Rationale for GSK3640254 + DTG

The sponsor has generated a growing body of evidence on the clinical efficacy, safety/tolerability, and resistance with a two ARV regimen containing DTG. As noted above, there is a clinical gap in these regimens with respect to the treatment experienced population (with DTG/3TC) or those patients with underlying NNRTI/NRTI resistance (either DTG/3TC or DTG/RPV).

Chronic exposure to NRTIs may lead to telomerase and mitochondrial dysfunction, processes that may lead to accelerated aging, lipodystrophy, steatohepatitis and other aging-related morbidities [Solomon, 2014]. A novel 2DR regimen combining DTG with GSK3640254 may limit the risk of many common adverse reactions associated with other ARV drugs. This regimen could be particularly valuable for patients with co-morbid conditions such as bone or cardiovascular disease, and due to both drugs' potential tolerability, as well as ease of use (once daily dosing and limited potential for drug-drug interactions). The proposed combination of GSK3640254 + DTG may address this clinical gap and warrants further investigation.

GSK3640254 + DTG may show a clinically advantageous profile in treatment-naïve people living with HIV-1. Understanding the efficacy, safety/tolerability, and resistance profile in the treatment naïve population (which has additional treatment options available and provides a high bar for clinical safety/tolerability) is necessary prior to investigating the combination in Phase 3 studies in treatment-experienced virologically suppressed adults living with HIV-1.

2.1. Study Rationale

The Sponsor proposes conducting this Phase 2b study, the primary objective of which is to evaluate the efficacy of GSK3640254 (initially at three doses: 100, 150, and 200 mg) + DTG relative to DTG + 3TC by analyzing the proportion of Virologic Responders (HIV-1 RNA <50 c/mL at Week 24). Secondary objectives are to evaluate: 1) longer term efficacy at Week 48, 2) safety/tolerability, and 3) cumulative resistance. The totality of this data (from a planned interim analysis onwards) would inform the basis of subsequent Phase 3 clinical trials in treatment-experienced virologically suppressed adults living with HIV-1.

2.2. Background

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

Previously, ViiV Healthcare studied a structurally similar MI, GSK3532795, in the Phase 2b study 205891. The Week 24 primary endpoint analysis showed GSK3532795 was not optimal for Phase 3 development due to gastrointestinal (GI) intolerability and treatment-emergent resistance. Specifically, a relatively higher rate of GI intolerability (predominately Grade 1-2 diarrhea in 38-61% of participants and abdominal pain in 8-22% of participants) and higher rate of nucleoside reverse transcriptase inhibitor (NRTI) resistance (6.5%) with clinically significant changes in GSK3532795 susceptibility was observed across all three GSK3532795 treatment arms [Morales-Ramirez, 2018]. Given these clinical and tolerability issues, ViiV Healthcare 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 supra-therapeutic doses: 1 healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The 2 participants received GSK3532795 240 mg twice daily and 240 mg once daily (QD) with food, respectively. These events were assessed as related to study intervention but were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric adverse events (AEs) in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia, abnormal dreams).

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

2.2.2. Preclinical Summary with GSK3640254

Nonclinical pharmacology and virology

Activity toward a panel of clinical isolates was similar among subtypes, with median 50% inhibitory effect (EC_{50}) values of 2.0 and 3.0 nM, for subtypes B and C, respectively, and 3 nM for subtypes A and CRF01_AE. GSK3640254 was active against 1 of 3 human immunodeficiency virus type-2 (HIV-2) isolates (EC_{50} = 2.5 nM). Based

upon in vitro potency, GSK3640254 is projected to demonstrate efficacy toward the majority of subtype B, C and CRF01_AE isolates at a trough concentration (C_{trough}) value of 150 nM. Data suggest that GSK3640254 may be used in combination therapies with agents from any of the nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase strand transfer inhibitor (INSTI) and protease inhibitor (PI) antiretroviral (ARV) classes.

Mechanism studies indicate that GSK3640254 blocks production of infectious virus by specifically inhibiting HIV-1 protease-mediated cleavage at the CA (p24)/SP1 junction. GSK3640254 specifically binds to purified HIV-1 VLPs (Ki 0.7 nM) and dissociates slowly, with a half-life of 6 h. These mechanistic studies confirm that GSK3640254 inhibits via a novel mechanism of action (MoA) that is distinct from current ARVs. The A364V amino acid substitution was the most common change selected by GSK3640254 in cell culture resistance selection experiments, appearing in several different group-specific antigen (Gag) polymorphic backgrounds.

Pharmacokinetics and product metabolism in animals

Following intravenous (IV) administration, GSK3640254 exhibited low systemic clearance, high volume distribution, and elimination half-lives of 5.06, 4.0, 18.7 and 5.3 h in mouse, rats, dogs and monkeys, respectively. GSK3640254 was eliminated mainly by direct glucuronidation followed by biliary excretion in bile-duct-cannulated (BDC) rats. Following repeat oral administration in the rat and dog, increases in systemic exposure to GSK3640254 was generally sub-proportional with dose. There was no or minimal accumulation of GSK3640254 after repeat dosing, and no consistent indication of a difference in exposure between genders.

Metabolic pathways observed in vitro included mono-oxidation, N-dealkylation and direct glucuronidation, with no unique metabolites generated in human liver microsomes or hepatocytes. In rat and dog plasma, GSK3640254 was either the only or the predominant drug-related component with minor oxidative metabolites.

Based on the predicted systemic exposures in human, there is a potential risk for GSK3640254 to act as a perpetrator of drug-drug interactions of substrates of OATP1B3 and MRP2. GSK3640254 was an inhibitor of UGT1A1 and clinical drug-drug interactions via this mechanism could be possible.

Toxicology

The primary target organ of toxicity in non-clinical studies with GSK3640254 was the stomach, with microscopic changes affecting parietal and chief cells in mice, rats and dogs. Due to microscopic changes in the stomach of rats at the lowest dose tested after 26 weeks, a no observed adverse effect level (NOAEL) in rats was unable to be determined. Microscopic findings in the stomach of rats were minimal to mild at the lowest observed adverse effect level (LOAEL) of 10 mg/kg/day (AUC = 18.9 µg.hr/mL), corresponding to 0.63-fold the predicted highest average human exposure. Following 39-weeks of dosing in dogs, the NOAEL for microscopic changes in the stomach was 0.2 mg/kg/day, and exposures were 0.28-fold the highest clinical exposure. Microscopic stomach changes were associated with increases in serum gastrin when evaluated in the

26- and 39-week studies in rats and dogs, respectively. All microscopic findings in the stomach of rats and dogs and changes in serum gastrin were shown to be reversible following a 4-week recovery period. Microscopic findings in the stomach were minimal to mild at the LOAELs of 10 mg/kg/day (AUC = 18.9 ug.hr/mL) and 1 mg/kg/day (AUC = 46.4 ug/hr/mL) in rats and dogs, respectively, corresponding to 0.63-fold and 1.6-fold highest clinical exposure. Potential effects in the stomach of humans are being investigated in a Stomach Substudy of the Phase 2b Study 208379, where HIV-1 infected treatment naïve adults are undergoing serial Esophagogastroduodenoscopy with biopsies of the stomach.

With correction for protein binding, compared to the IC_{50} for the hERG/IKr potassium channel, there is a 15.8-fold margin above the predicted average clinical maximum concentration (C_{max}) exposure for the highest dose. Exposure where a minimal increase in QT interval was seen in a single dog in the single-dose safety pharmacology study in telemeterized dogs was 3.6-fold higher than the predicted C_{max} at the highest dose. In addition, there were no effects on electrocardiogram (ECG) parameters in dogs given up to 25 mg/kg/day for 4 weeks at 19.3-fold above the predicted average C_{max} at the highest dose.

2.2.3. Key Clinical Data on GSK3640254 to date

A summary of safety data from the completed clinical studies performed to date is succinctly described here for convenience.

- 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 urticaria and maculopapular rash led to discontinuation.
- Treatment emergent drug-related Grade 2-4 AEs included: 1) Headache (2 participants both Grade 2; one participant in Studies 207187 and 208132, each), 2) Nausea (2 participants both Grade 2; one 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 with elevated transaminases, 5 of which were reported as AEs). Subsequent analysis in Study 208135 showed no PK/PD relationship with either GSK3640254 or Portia and elevated transaminases. The elevated transaminases were likely due to the recent initiation of hormonal contraception in study participants.
- Treatment-related AEs reported in more than 1 study included headache (Studies 207187, 208131, and 208132) and nausea (Studies 207187 and 208132).
- Across studies, low grade GI intolerability has been observed: the majority of AEs 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 Investigator Brochure and the supporting Clinical Study Reports (available upon request).

2.2.4. Key Phase 2a (Study 208132) Clinical Data on GSK3640254

Study Design

Study 208132 was a two-part, Phase 2a, global, multicenter, randomized, partially-blind (Sponsor unblinded), placebo-controlled, adaptive clinical trial to evaluate the antiviral effect, safety, tolerability and PK/ PD of GSK3640254 in ART-naïve adults living with HIV-1. Part 1 evaluated placebo (n=2 participants) and two active doses (10 and 200 mg QD) of GSK3640254 in two dose arms (n=6 participants in each dose arm) – all given for 10 days. Due to the mitigation of treatment emergent A364A/V and A364V genotypic changes seen in the 200 mg arm (described below), Part 2 evaluated placebo (n=2 participants) and three active doses (40, 80, and 140 mg QD) of GSK3640254 in three dose arms (n=6 participants in each dose arm) – only given for 7 days.

Primary Objective: Antiviral decline after 7 to 10 days of monotherapy

Of the 34 randomized participants in Part 1 and 2 combined, the average age was 32 years. Two females were randomized. The short-term antiviral response is shown in Table 1.

Table 1 Summary of Plasma HIV-1 RNA (log 10 c/mL) Change from Baseline and Maximum Decline from Baseline in 208132

	GSK3640254					Placebo	
	10 mg Part 1	40 mg Part 2	80 mg Part 2	140 mg Part 2	200 mg Part 1	Part 1	Part 2
	N = 6	N = 6	N = 6	N = 6	N = 6	N = 2	N = 2
Baseline							
Mean	4.187	4.672	4.433	4.533	4.820	4.245	4.750
Median	4.180	4.690	4.255	4.455	4.825	4.245	4.750
Change from Baseline at Day 8, 9, or 10 (Part 1) or Day 8 (Part 2)							
Mean	-0.137	-1.178	-1.015	-1.450	-1.700	0.155	0.150
Median	-0.125	-1.145	-1.035	-1.410	-1.570	0.155	0.150
SD	0.3730	0.4358	0.3299	0.2353	0.3447	0.0354	0.2263
Maximum Change from Baseline within Study Period							
Mean	-0.363	-1.178	-1.015	-1.488	-2.013	-0.205	-0.030
Median	-0.280	-1.145	-1.035	-1.445	-1.960	-0.205	-0.030
SD	0.2519	0.4358	0.3299	0.2671	0.3292	0.2616	0.1273

Secondary Objective: Assessment of Safety/Tolerability

There were no deaths. There were two SAEs: 1) unrelated severe dilated congestive cardiomyopathy (Grade 3), and 2) anal abscess (Grade 1). The participant with unrelated severe dilated congestive cardiomyopathy also had an AE of unrelated idiopathic myocarditis (Grade 3). Both SAEs and the AE were unrelated to study medication. Note, the participant with congestive cardiomyopathy received GSK3640254 10 mg. An in-depth discussion of this participant's clinical course is located in Section 5.3.2.5. of the IB.

There were no AEs which led to discontinuation. There were 9 participants with 14 related AEs. Of these 14, 11 were Grade 1 (mostly gastrointestinal in nature) and three were Grade 2 (rash maculo-papular, abdominal pain, and nausea).

Of the 34 participants randomized, 22 participants developed 50 individual AEs. There were 7 participants with seven Grade 2 AEs: abdominal pain (related), nausea (related), pyrexia, spine pain, rash maculo-papular (related), headache, and neutropenia. The remaining AEs are shown in Table 2. The most frequent AEs occurred in the Infections/Infestations SOC (8 participants). The most frequent individual AE was headache (4 participants). Although not shown, all GI AEs and Neuropsychiatric AEs were less than 1 day in duration except: 1) one participant had a headache (Grade 1) from Study Day 1-2, 2) one participant had diarrhea and vomiting (both Grade 1) from Study Day 4-9, and 3) one participant had constipation (Grade 1) from Study Day 1-5.

Table 2 Summary of All Adverse Events by Preferred Term (Safety Population)

Preferred Term	GSK 10 mg (N=6)	GSK 40 mg (N=6)	GSK 80 mg (N=6)	GSK 140 mg (N=6)	GSK 200 mg (N=6)	Placebo (N=4)	Total (N=34)
Any Event	**3 (50)**	**5 (83)**	**4 (67)**	**5 (83)**	**5 (83)**	**0**	**22 (65)**
Headache	0	1 (17)	0	1 (17)	2 (33)	0	4 (12)
Diarrhea	1 (17)	1 (17)	0	0	1 (17)	0	3 (9)
Oropharyngeal pain	0	0	0	1 (17)	2 (33)	0	3 (9)
Nasopharyngitis	0	0	0	0	2 (33)	0	2 (6)
Vomiting	1 (17)	0	0	0	1 (17)	0	2 (6)
Abdominal pain	0	0	2 (33)	0	0	0	2 (6)
Lymphadenopathy	1 (17)	0	0	0	1 (17)	0	2 (6)
Anal abscess	0	0	0	1 (17)	0	0	1 (3)
Meningococcal infection	1 (17)	0	0	0	0	0	1 (3)
Pharyngitis	0	0	0	0	1 (17)	0	1 (3)
Upper respiratory tract infection	0	0	0	0	1 (17)	0	1 (3)
Urinary tract infection	0	0	0	1 (17)	0	0	1 (3)
Viral infection	0	1 (17)	0	0	0	0	1 (3)
Constipation	0	0	0	1 (17)	0	0	1 (3)
Nausea	1 (17)	0	0	0	0	0	1 (3)
Migraine	0	0	1 (17)	0	0	0	1 (3)
Presyncope	0	1 (17)	0	0	0	0	1 (3)
Asthenia	0	0	0	0	1 (17)	0	1 (3)
Fatigue	0	1 (17)	0	0	0	0	1 (3)
Nodule	0	0	1 (17)	0	0	0	1 (3)
Pyrexia	0	0	0	0	1 (17)	0	1 (3)
Catarrh	0	0	0	0	1 (17)	0	1 (3)
Epistaxis	0	1 (17)	0	0	0	0	1 (3)
Neutropenia	0	0	1 (17)	0	0	0	1 (3)
Pain in extremity	0	0	1 (17)	0	0	0	1 (3)
Spinal pain	1 (17)	0	0	0	0	0	1 (3)
Dermatitis atopic	0	0	1 (17)	0	0	0	1 (3)
Pruritus	0	0	0	1 (17)	0	0	1 (3)
Rash maculo-papular	0	0	0	1 (17)	0	0	1 (3)
Congestive cardiomyopathy	1 (17)	0	0	0	0	0	1 (3)
Myocarditis	1 (17)	0	0	0	0	0	1 (3)
ALT increased	1 (17)	0	0	0	0	0	1 (3)
AST increased	1 (17)	0	0	0	0	0	1 (3)
Hyperglycaemia	1 (17)	0	0	0	0	0	1 (3)
Insulin resistance	1 (17)	0	0	0	0	0	1 (3)
Vitamin D deficiency	1 (17)	0	0	0	0	0	1 (3)
Chromaturia	1 (17)	0	0	0	0	0	1 (3)

Source Data: Table 3.2 of CSR 208132

There were no abnormal clinically significant arrhythmias or corrected QT interval (QTc) prolongations (values >500 msec or increases >60 msec from baseline) observed for any participant. There were no clinically significant trends in vital signs, chemistry laboratory values, or hematology laboratory values across the arms.

CCI

Secondary Objective: Characterization of PK Profile

GSK3640254 PK parameters derived based on nominal times following once-daily administration of 10 mg and 200 mg once daily for 10 days were determined on Day 1 (Part 1 and 2) and either Day 8-9 (Part 1) or Day 7 (Part 2) (Table 3). Following once-daily administration of GSK3640254 over 10 mg to 200 mg dose range with a moderate fat meal, Day 1 median T_{max} ranged between 3.00 – 5.50 hours. Variability in the PK parameters [% between-participant coefficient of variation (CVb)] ranged from 19% to 52%.

Steady-state (Day 8-9 or 7 for Part 1 and Part 2, respectively) median T_{max} ranged between 4.00 h and 5.50 h. Variability in the PK parameters [%CVb] was low to moderate, ranging from 19.5% to 47%.

Although the sample size is small, GSK3640254 demonstrated generally dose-proportional PK over the dose range studied (10 – 200 mg). Consistent with antiviral decline described above, the PK parameters of: a) 40 and 80 mg approximated each other, and b) 140 and 200 mg approximated each other. There were three participants in the 80 mg arm who had exposure similar to that observed at 40 mg dose (data not shown).

Table 3 Summary Statistics of Day 1 and Day 8-9 (Part 1) or Day 7 (Part 2) PK Parameters Following Multiple Daily Dose Administration of GSK3640254 in Study 208132

		10 mg n=6	40 mg n=6	80 mg n=6	140 mg n=6	200 mg n=6[1]
	PK Parameter	Geometric Mean [CVb%] (95% CI)				
Day 1	AUC(0-24) (µg*h/mL)	0.695 [13.5] (0.588, 0.821)	3.25 [31.7] (2.35, 4.50)	6.12 [38.8] (4.13, 9.07)	14.0 [36.6] (9.67, 20.4)	12.4 [91.3] (5.48, 28.0)
	Cmax (µg/mL)	0.059 [177.4] (0.017, 0.207)	0.232 [30.5] (0.169, 0.317)	0.433 [33.6] (0.307, 0.610)	0.918 [41.5] (0.604, 1.395)	0.938 [82.3] (0.441, 2.00)
	Tmax (h) (median)[range]	2.93 [0.00, 5.00]	4.42 [3.97, 8.00]	4.08 [2.95, 6.17]	5.51 [3.00, 6.25]	5.53 [3.92, 8.05]
Steady State [2]	AUC(0-24) (µg*h/mL)	0.908 [44.7] (0.580, 1.422)	7.46 [26.8] (5.66, 9.84)	11.8 [26.7] (8.98, 15.6)	29.3 [27.9] (22.0, 39.0)	27.9 [18.4] (23.1, 33.8)
	Cmax (µg/mL)	0.055 [41.3] (0.036, 0.083)	0.469 [20.6] (0.379, 0.581)	0.747 [23.7] (0.585, 0.955)	1.86 [26.0] (1.42, 2.43)	1.86 [19.5] (1.51, 2.27)
	Tmax (h) (median)[range]	4.02 [1.87, 5.00]	4.06 [2.00, 8.00]	4.58 [4.00, 5.18]	4.08 [2.92, 5.20]	5.48 [3.00, 6.20]
	Ctau (µg/mL)	0.027 [47.0] (0.017, 0.043)	0.219 [30.1] (0.161, 0.298)	0.360 [31.1] (0.262, 0.495)	0.798 [34.1] (0.563, 1.131)	0.703 [29.6] (0.519, 0.953)

CI = Confidence interval

[1]One participant In the 200 mg group has been excluded from PK analysis for day 1 due to vomiting within 1x tmax post-dose

[2]Steady State was measured at Visit 5/6 (Day 8/9 in Part 1 vs Day 7 in Part 2) [Based on FTIH study, mean half-life ranges between 21 h – 28 h]

The key PK modelling and simulation data from Study 208132 is summarized in the dose justification in Section 4.3.

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 corrected QT interval (QT), neuropsychiatric safety, skin and subcutaneous tissue disorders, and treatment emergent virologic resistance.

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 relatively healthy

treatment-naïve adults living with HIV-1 who will receive clinical, ECG, and laboratory evaluations during their participation.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK3640254 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2018N379610_02].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
Study Intervention 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 QT interval (up to 20 ms) occurred primarily in 1 dog given 17 mg/kg. Later, there were no GSK3640254-related effects on electrocardiogram (ECG) parameters in dogs given up to 25 mg/kg/day for up to 39 weeks. In Study 207187 (MAD) the concentration-QTc analysis, a QTcF effect above 10 ms 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 trial-based Stopping Criteria for QTcF prolongations: values >500 ms or increases >60 ms 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 7.1.3). As noted in Section 7.1.3, 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.
Gastrointestinal 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	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms (see Section 5.2)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	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 IB, the rates of all GI AEs (all Grade 1 regardless of relationship) in the MAD portion of Study 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).	Participants will undergo continuous evaluation for adverse events 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).
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). To explore the monitoring of gastric toxicity, a subset of ~7 participants in each arm from the 208379 study will take part in the Optional Stomach Sub-study and will undergo EGD with Biopsy of the greater and lesser curvature (for subsequent histopathologic examination) along with a measurement of Serum Biomarkers. There is no clinical approach for evaluating gastric toxicity in Study 212483.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
Neurologic/psychiatric safety	Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in a TQT study. From a Neurologic and Psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies, mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. While summarized in the IB, the rates of all Nervous system and Psychiatric AEs in the MAD (Study 207187 FTIH) ranged from 24-57% and 0-17%, respectively across doses (50-320 mg x 14 days) without any trend. No GSK3640254 clinical trial has observed SAEs of acute psychosis or homicidal/suicidal ideation.	Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment and the eC-SSRS tool) in participants. Continuous evaluation for adverse events during their participation in the trial including direct AE inquiry as noted in Section 1.3. Participants will also provide responses to the eC-SSRS throughout the study. Ultimately, in the event of a new onset suicidality ideation or behavior (SIB), 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. 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).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		The participant informed consent form includes information on the risk of depression and suicidal ideation and behaviour.
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 adverse events during their participation in the trial supplemented by the use of physical exams. Protocol includes individual participant stopping criteria, including any Grade 3 or higher rash, or Grade 2 rash with any systemic signs, allergic symptoms, or if mucosal involvement develops. (see Section 10.9.3).
Study Intervention DTG		
Hypersensitivity reaction (HSR) and rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) 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. Guidelines for the management of HSR are provided in Section 10.9.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		Also see Section 7.1, Discontinuation of Study Intervention. Specific/detailed toxicity management guidance is provided for rash (Section 10.9.3.1) The participant informed consent form (ICF) includes information on this risk and the actions participants should take in the event of a HSR or associated signs and symptoms.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For participants with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART, along with inadequate therapy for HBV 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/ABC/3TC. 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	Participants meeting any of the following criteria during the screening period are excluded from participating. • Alanine aminotransferase (ALT) ≥3 times the-upper limit of normal (ULN) or ALT ≥2xULN and bilirubin ≥1.5x ULN • Infection with Hepatitis B or Hepatitis C, as described in the Exclusion Criteria (See Section 5.2) Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 10.9.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	likely and the role of DTG-containing regimens cannot be ruled out particularly in those involving DTG.	
Psychiatric disorders	Psychiatric disorders including suicidal ideation and behaviours are common in people living with HIV. Events of suicidal ideation, attempt, behaviour and completion were observed in clinical studies of DTG, primarily in participants with a pre-existing history of depression or other psychiatric illness.	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 adverse events 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 (SIB), 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. 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).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
		The participant informed consent form includes information on the risk of depression and suicidal ideation and behaviour.
Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 6.8.1).
Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with inhibition of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 10.9.6). Creatinine clearance is calculated in all participants prior to initiating therapy and renal function (creatinine clearance and serum phosphate) will be monitored at all subsequent study visits.
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 dolutegravir-containing regimens from the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens from the time of conception (Prevalence Difference 0.09%; 95% CI -0.03-0.30).	1. Participants who are female at birth who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 2. Participants who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	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 dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy. Data analysed 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 dolutegravir. 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,	pregnancy avoidance methods, will have study treatment discontinued and will be withdrawn from the study. 3. Participants of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 4. Pregnancy status is monitored at every study visit

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	were identified. Dolutegravir was shown to cross the placenta in animals.	
Study Intervention 3TC		
Renal Function	3TC is eliminated by renal excretion and exposures increase in participants with renal dysfunction. 3TC is not recommended to treat participants with a creatinine clearance <50 mL/min.	Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 10.9.6). Creatinine clearance is calculated in all participants prior to initiating therapy and renal function (creatinine clearance and serum phosphate) will be monitored at all subsequent study visits. Participants with creatinine clearance <50 mL/min are excluded from participation in this study. In addition, if an on-treatment estimated GFR of <50 mL/min is confirmed, then study medications will be discontinued and the participant withdrawn.
HIV-1 Infection/Patient Population		
HIV Resistance to GSK3640254 and other on-study treatments	There is an intrinsic risk of resistance (genotypic changes or decreased phenotypic susceptibility) to any developmental ARV (or the ARVs which are co-administered).	As described above, this risk will be mitigated using the following approaches.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a,b]
	Note: Data from Study 208132 (Phase 2a POC) showed a decline in HIV-1 RNA and reasonable PK profile. However, some participants receiving GSK3640254 had treatment emergent resistance mutations associated with maturation inhibitors observed on or after Day 11 (after 10 days of receiving GSK3640254 monotherapy). However, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, or integrase inhibitors) was observed as there is no known cross-resistance between maturation inhibitors and other classes of ARVs.	1) HIV-1 RNA at Week 2 will be obtained to demonstrate a decline relative to Day 1. 2) All participants will have their HIV-1 RNA monitored at frequent intervals and have criteria for resistance testing based upon the development of Protocol Defined Virologic Failure (Section 7.1.1)

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected participants). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study intervention, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

b. Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (GSK)/ViiV Healthcare Safety Review Team meetings. This will include in-stream review of data from this clinical trial on a routine basis.

2.3.2. Benefit Assessment

Participants in this clinical study may benefit from receiving a combination of ARVs containing GSK3640254. Data from the Phase 2a study does show a PK/PD (decline in HIV-1 RNA) relationship (described in detail in Section 4.3). Thus, GSK3640254 may contribute to a decline in HIV-1 RNA (and maintenance of suppression) when administered with DTG. A decline in HIV-1 RNA is directly associated with a reduction in HIV/AIDS related morbidity/mortality.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize the potential risks to participants in this study, the potential risks identified in association with GSK3640254 + DTG are justified by the anticipated benefits that may be afforded to participants with HIV-1 infection achieving and maintaining virologic suppression.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate antiviral efficacy of GSK3640254 + DTG, relative to DTG + 3TC at Week 24 in HIV-1-infected, ART-naïve participants	• Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 using the FDA snapshot algorithm
Secondary	
• To evaluate the antiviral activity of GSK3640254 + DTG relative to DTG + 3TC at Week 48	• Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm • Absolute values and changes from baseline in HIV-1 RNA through Weeks 24 and 48 • Absolute values and changes from baseline in CD4+ T-cell counts through Weeks 24 and 48
• To evaluate safety and tolerability of GSK3640254 when given in combination with DTG, relative to DTG + 3TC	• Frequency of SAEs, Deaths and AEs leading to Discontinuation through Weeks 24 and 48 • AEs of special interest (AESIs) through Weeks 24 and 48

Objectives	Endpoints
• To assess the development of viral resistance to GSK3640254 and other on-study ART in participants experiencing virologic failure through Week 48	• Changes in genotypic and/or phenotypic profiles of virus compared to baseline
• To assess the steady-state exposure of GSK3640254 when given in combination with DTG	• The steady-state plasma PK parameters of GSK3640254 will be assessed based on Sparse PK sampling through Week 48
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

Study 212483 is a Phase IIb, randomized, multicentre, double-blind, active-controlled, parallel group study to be conducted in approximately 80 ART-naïve adults living with HIV-1. Participants will be stratified by screening plasma HIV-1 RNA, by <100,000 c/mL or ≥100,000 c/mL, and randomized to one of the three doses of blinded GSK3640254 (100, 150, or 200 mg) or a reference arm of blinded 3TC – each in combination with open label DTG (See Section 1.2). The study will include a Screening Phase (to a maximum of 30 days), a double-blind Randomized Phase (Day 1 to Week 24) and an open-label Randomized Phase (Week 24 to Week 52). The study will be double-blind through the Week 24 primary endpoint.

Another Phase 2b study, 208379, has been ongoing since November 2020. Study 208379 is a Phase 2b dose range finding trial where HIV-1 infected treatment naïve adults are randomized to either one of three experimental doses of GSK3640254 (also 100, 150, and 200 mg) or DTG – in combination with investigator selected dual NRTI therapy. Study 208379 contains at least one interim analysis (of efficacy and safety/tolerability) performed by an IDMC using data from the first ~50 participants who have completed their Week 12 visit. The primary endpoint is the proportion of virologic responders at Week 24.

Study 212483 started recruitment in advance of the initial 208379 IDMC review. The 208379 IDMC issued a no-action letter on 06-OCT-2021, so Study 212483 continued to randomize participants to all three experimental arms.

This study will utilize an Independent Data Monitoring Committee (IDMC) to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of participants and to protect the scientific validity of the study. An ad-hoc review of data by the IDMC will be triggered when the number of participants exceeds thresholds pre-specified in the IDMC charter for either: protocol-defined virologic failure criteria or number of safety/tolerability events. In addition, the IDMC will be triggered at a timepoint prior to the primary endpoint. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter. If a rate for PDVF or safety/tolerability events trigger review by the Study 212483 IDMC, the following potential implications may hold true for originally randomized participants (participants who are not yet randomized would be managed as described immediately above):

1) If the 212483 IDMC recommends termination of the 100 mg arm (e.g. sub-therapeutic efficacy): Study 212483 will discontinue all participants in the 100 mg experimental arm and the PI will transition them to the SOC cART.

2) If the 212483 IDMC recommends termination of either 150 or 200 mg arm: Study 212483 will re-randomize all participants on the 150 or 200 mg experimental arms, respectively to the remaining experimental arms. Termination of the experimental 150 mg dose alone is clinically unlikely (see Scenario 3 and 4 immediately below).
3) If the 212483 IDMC recommends termination of both 150 and 200 mg arms (e.g. safety/intolerability): Study 212483 will switch all participants on the 150 and 200 mg experimental arms to the remaining experimental 100 mg arm.
4) If the 212483 IDMC recommends termination of both 100 and 150 mg arms due to subtherapeutic efficacy: Study 212483 will discontinue all participants in the 100 and 150 mg experimental arm and the PI will transition them to the SOC cART.
5) If the 212483 IDMC recommends termination of both 100 and 200 mg arms due to subtherapeutic efficacy and safety/tolerability, respectively: Study 212483 will discontinue all participants in the 100 mg experimental arm and the PI will transition them to the SOC cART. Study 212483 will re-randomize all participants on the 200 mg experimental arm to the remaining experimental 150 mg arm.

	Possible Implication for Originally Randomized Participants		
Possible Decision	**100 mg**	**150 mg**	**200 mg**
No doses D/C	All doses continue		
100 mg D/C	100 mg Transition to SOC	150 and 200 mg doses continue	
150 mg D/C	This is a unique and unlikely situation and would be managed as below (100 and 150 mg D/C due to subtherapeutic efficacy OR 150 and 200 mg D/C due to safety/tolerability)		
200 mg D/C	100 mg Continues	150 mg Continues	200 mg re-randomized to remaining experimental arms
100 and 150 mg D/C	100 and 150 mg Transition to SOC		Continues
100 and 200 mg D/C	100 mg Transition to SOC	150 mg Continues	200 mg switched to remaining 150 mg arm

	Possible Implication for Originally Randomized Participants	
150 and 200 mg D/C	Continues	150 and 200 mg switched to remaining 100 mg arm
All doses D/C	All doses Transition to SOC	

Study 208379 Week 24 Primary Analysis of Efficacy, Safety/Tolerability, & Resistance

The Sponsor's 208379 Study team will evaluate the totality of unblinded data for efficacy, safety/tolerability, and resistance on one, two, or three experimental arms (the variable number of arms reflects potential for 208379 IDMC recommendations). The review of this data (relative to pre-established internal Go/No-Go criteria) will result in the selection of an optimal continuation dose which will be used on all participants in the experimental arms of Study 208379 after the last participant completes their Week 48 visit. Once the optimal continuation dose selection is made in Study 208379, all participants on remaining experimental arms in Study 212483 will be handled as follows:

1) Study 212483 participants on the optimal one GSK3640254 dose arm (selected from study 208379): these participants will continue to receive their original blinded dose until the Study 212483 primary endpoint.
2) Study 212483 participants on the non-optimal GSK3640254 dose arms (not selected from study 208379): participants will shift from their current dose to the optimal GSK3640254 dose. The blinded drug supply will be provided until the study 212483 Week 24 primary endpoint.

Approximately 160 participants will be screened to achieve approximately 80 randomly assigned to one of 4 arms of the study interventions, approximately 20 per GSK3640254 arm, and approximately 20 in the DTG + 3TC Reference Arm. Targets to increase diversity will be defined at a country level in the study recruitment plans.

The study will include:

- A Screening Phase to a maximum of 30 days
- A Double-blind Randomized Phase (first participant Day 1 to last participant Week 24)
- An Open-label Randomized Phase (last participant Week 24 to last participant Week 52)

At Day 1, participants will be randomized to one of the following study treatment arms. All participants will receive 5 bottles of study treatment (1 with DTG tablets, 3 with GSK3640254 or matching placebo tablets and 1 with 3TC or matching placebo capsules) to maintain the study blind through last participant Week 24. Participants will take 1 tablet/capsule from each bottle at each dose.

- Arm 1: Blinded GSK3640254 100 mg + Unblinded DTG 50 mg
- Arm 2: Blinded GSK3640254 150 mg + Unblinded DTG 50 mg
- Arm 3: Blinded GSK3640254 200 mg + Unblinded DTG 50 mg
- Arm 4: Unblinded DTG 50 mg + Blinded 3TC 300 mg

Once the study enters the open-label randomized phase, participants will take only the number of tablets required to make up their dose. Participants in the DTG + 3TC arm will switch from over-encapsulated 3TC to open-label 3TC tablets.

4.1.1. Screening Period

Assuming a screen failure rate of 50%, approximately 160 participants will be screened for this study to randomize approximately 80 eligible participants.

Participants will enter a Screening period of up to 30 days.

At the Screening visit, fasting blood samples and urine will be collected, an ECG will be done, and participants will be asked to provide responses to the eC-SSRS Baseline assessment about thoughts and feelings throughout their entire lifetime and current experience (within the last 2 months).

Prohibited Medications (Section 6.8.1.2) will be reviewed for any medications the participant is taking that need to be stopped as much as 4 weeks prior to the first dose.

Participants may be rescreened once (See Section 5.4). However, participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be rescreened.

4.1.2. Treatment Period

Visits may be conducted within a window of ± 2 days. The exception to this is the Week 2 visits, which may be conducted between Days 11- 14.

Any interruption in therapy during the treatment period of 3 or more consecutive days, for any reason, must be discussed with the ViiV Medical Monitor prior to resumption of therapy, if possible. If therapy was resumed without prior approval (i.e., if the PI was not aware at the time of the missed doses), the Investigator should contact the ViiV Medical Monitor upon becoming aware.

Participants will be asked to complete a diary card that will capture key dosing times prior to visits that collect PK samples as well as dates of any missed doses that can be recalled. Site staff will perform pill counts to check compliance. At every visit site staff will discuss the importance of adherence, ensuring participants understand the risk for developing resistance that comes with non-compliance.

Dose administration on all arms requires participants to dose in the morning (due to study PK and/or post-dose ECG requirements and for consistency of daily dosing), and at/near the same time each day (see the SRM for guidance).

Study intervention administration during the double-blind phase of the study should be with a low-fat meal (see Section 5.3.1). Thereafter, during the open-label phase, only dose administration with GSK3640254 requires participants to be dosed with a low-fat meal.

All subjects will provide samples for Sparse PK at Weeks 2, 4, 8, 12, 24 and 48. At each of these visits, a PK sample is drawn at the beginning of the visit with all of the other blood samples.

The visit at Week 2 is to be done by all study participants (for collection of HIV-1 RNA, plasma for storage, pre-dose PK, a pre-dose ECG and all 3 post-dose ECGs).

Fasting requirements:

- Participants need to fast for a minimum of 8 hours prior to the visits at which lipids are collected. An overnight fast is preferred.

4.1.2.1. Day 1 through Week 24

Participants will be randomized to either: one of the three blinded, QD, oral GSK3640254 dose regimens (approximately 20 participants per treatment arm, each in combination with DTG), or to the active control Reference Arm of DTG + 3TC (approximately 20 participants).

- Arm 1: Blinded GSK3640254 100 mg + unblinded DTG 50 mg
- Arm 2: Blinded GSK3640254 150 mg + unblinded DTG 50 mg
- Arm 3: Blinded GSK3640254 200 mg + unblinded DTG 50 mg
- Arm 4: Unblinded DTG 50 mg + blinded 3TC 300 mg

On Day 1, there are several pre-dosing assessments and procedures, then ECGs are also required 2, 4 and 6 hours post-dose. ECGs are also required 2, 4 and 6 hours post-dose at Week 2.

Participants will be seen in-clinic for study visits approximately every 4 weeks. At these clinic visits, blood and urine will be collected, ECG(s) will be done at some visits, and participants will be asked to provide responses to the eC-SSRS questions about their thoughts since the last visit (See Section 1.3).

4.1.2.2. Week 24 through 52

Participants will be seen in-clinic for study visits approximately every 4 weeks (See Section 1.3).

4.1.2.2.1. Potential cART Reimbursement after Last Dose of Study Treatment

Sponsor recognizes that the clinical goal is for all participants to achieve and maintain virologic suppression. When a participant is discontinued from the trial early, whether

they are a Virologic Non-Responder at Week 24 or they are withdrawn early for any other reason, there may be situations where sites may be reimbursed for up to a 6-week supply of Investigator selected/prescribed antiretroviral medication to facilitate the transition of participants to non-study cART. Any brief duration of reimbursement longer than 6 weeks, expected to be in individual and rare circumstances, may be considered with Sponsor.

Specific direction will be provided by GSK/ViiV, who will determine for which country(ies) this is not a viable option, e.g., where reimbursement is not allowed by local regulations, or where acquisition of cART can be obtained without delay.

4.1.3. Follow-up

After the last dose, when a participant withdraws early (at any point prior to the end of the study, including Virologic Non-responders at Week 24), participants will be required to be seen in-clinic for a follow-up visit between 2 to 4 weeks after their Early Withdrawal visit. These data comprise an essential evaluation that needs to be done before discharging any participant from the study.

Beyond this follow-up visit (outside of the study), all AEs, SAEs and clinically relevant vitals, ECG findings, and lab abnormalities will be followed towards acceptable clinical resolution.

Participants who are withdrawn for reasons of safety should continue to be followed even beyond the study final, follow-up visit (outside of the study) to assess the outcome of the safety event that triggered discontinuation of study intervention (as determined by the Investigator).

An in-clinic Follow-Up visit will be conducted 2-4 weeks after the last dose of study medication for participants with ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit (Week 52). Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality).

Any participant who continues to access to study treatment after their Week 52 visit and who subsequently discontinues study treatment for any reason will be asked to attend a discontinuation/withdrawal visit and a follow-up visit. They will undergo the same procedures and assessments as for the Early Withdrawal and follow-up visits required for participants who discontinue or withdraw during the main study (see Section 1.3). Discontinuation/withdrawal visits during continued access will be captured on distinct eCRF pages to those from the main study.

4.1.4. Study Completion

For study status purposes, a participant is considered to have completed the study if they completed the Week 52 visit. The Follow-Up visit is not required for successful completion of the study.

- To provide continued access to an investigational drug to participants deriving therapeutic benefit, participants who have successfully completed 52 weeks of treatment may be given the opportunity to continue to receive their study treatment. During the blinded randomized phase: that could be non-optimal GSK3640254 + DTG, optimal GSK3640254 + DTG, or 3TC + DTG).
- During the open label randomized phase:
    - Any participant who received 3TC + DTG beyond their individual Week 52 visit will discontinue from the study and be transferred to locally available standard of care treatment.
    - Any participant who received GSK3640254 + DTG beyond their individual Week 52 visit will be switched to a single optimal dose of GSK3640254 once it is determined from the ongoing Study 208379. After this occurs, participants who continue to receive GSK3640254 + DTG beyond their individualized Week 52 will have the option to continue on open label optimal dose GSK3640254 + DTG until either they or their healthcare provider decide to discontinue study treatment or until GSK3640254 + DTG is receives local marketing authorization and is commercially available).
- Continued access to GSK3640254 + DTG in Study 212483 may occur, as described above, provided all of the following conditions are met:
    - There is evidence of continued clinical benefit for the participant, and
    - There are no comparable alternative treatment options available, and
    - Such provision of GSK3640254 + DTG is permitted under local laws and regulations.

Continued access to an investigational drug will cease if the participant no longer derives clinical benefit from receipt of GSK3640254 + DTG; the participant meets a protocol-defined reason for discontinuation; or the development of GSK3640254 + DTG is discontinued.

Importantly, study 212483 may be terminated early by the CMO at least if either of the two situations below occur:

a) This study 212483 IDMC recommends discontinuing all remaining experimental arms,

b) Results from study 208379 primary analysis prompt a development decision (e.g. termination) for GSK3640254.

4.2. Scientific Rationale for Study Design

Based on available GSK3640254 data, including in vitro virology, PK, antiviral activity/resistance, and safety/tolerability data from completed clinical trials, doses 100 mg, 150 mg and 200 mg QD are anticipated to provide adequate antiviral activity/efficacy and be well-tolerated (in combination with DTG). As described earlier, these are the same three doses used in the ongoing Phase 2b dose-range finding trial, Study 208379, in HIV-1 infected treatment naïve adults. The primary endpoint will assess efficacy by determining the proportion of virologic responders (participants with plasma

HIV-1 RNA <50 c/mL at Week 24). HIV-1 RNA is highly predictive of meaningful clinical benefit [U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2015].

The reference arm (DTG + 3TC) chosen for this study is an accepted regimen for initiation of antiretroviral therapy in treatment guidelines [European AIDS Clinical Society (EACS) Guidelines, 2020; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2021] and, as such, is considered appropriate for this trial.

4.2.1. Participant Input into Design

Community experts participated in review of the protocol study design and entry criteria. Based on feedback received, text was added to align with our company position to clarify that receipt of a SARS-CoV-2 vaccine that has received emergency, conditional, or standard market authorization is allowed.

4.3. Justification for Dose

The planned doses of GSK3640254 for this Phase 2b study (100 mg, 150 mg, and 200 mg QD administered with food) were selected based on population PK and exposure-response (E-R) modelling and clinical trial simulations of antiviral effect as described in this section. The doses were targeted to achieve a minimum of 75% of maximum effect predicted at day 8 and to maintain steady-state Cτ above the 3-times protein binding-adjusted EC90 (3xPBAEC90) target of 0.11 µg/mL (in-vitro EC90 value for *in-vitro* virus containing R361K/V362I/L363M substitutions) in 95% of the participants.

A population pharmacokinetic model was developed using the single dose (1 – 400 mg) and multiple dose (50-320 mg QD for 14 days) data from healthy participants from the FTIH study 207187, as well as the multiple dose data in participants living with HIV-1 (10 mg – 200 mg QD for 7-10 days from study 208132). All doses were administered with a moderate-fat meal. The pharmacokinetics of GSK3640254 (given with food) was described by a two-compartment model with sequential zero-order absorption (in the depot compartment) followed by first order absorption (from depot to the central compartment) and first order elimination. Inter-individual variability was estimated on the apparent oral clearance (CL/F), apparent volume of distribution of the central compartment (V2/F), intercompartmental clearance (Q/F), absorption rate constant (Ka), and duration of the zero-order process (D1). The CL/F and V2/F were scaled using fixed allometric coefficients of 0.75 and 1, respectively. Weight was found to be a significant covariate on Ka. In addition, 'STUDY' (i.e. 207187 vs. 208132, as a surrogate for subject type and GSK3640254 salt differences) was also found to be significant covariates on bioavailability (F was ~27% lower in the FTIH study compared to that from the PoC). Evaluation of the post-hoc individual estimates of Cmax, AUC and Cτ indicated that model-estimated PK parameters were comparable to the observed values.

The objective of the E-R analysis was to characterize the relationship between antiviral activity and exposure of GSK3640254 in participants living with HIV-1, and to determine the effect of key covariates (including baseline EC50, baseline HIV-1 RNA, baseline CD4 and CD8 T-cell counts) on GSK3640254 antiviral activity. The E-R

analysis was conducted using the data from the Phase 2a study 208132 (up to day 8/9 [Visit 5] in Part 1 and up to day 8 [Visit 6] in Part 2. All doses were administered with a moderate-fat meal. The decline in HIV-1 RNA over 7 or 10 days (and the treatment emergent genotypic and phenotypic changes) in treatment naïve adults living with HIV-1 is described in Section 2.2.4.

The E-R was assessed via an inhibitory Emax model using the observed average steady-state Cτ and maximum viral load decline from baseline. None of the screened covariates were found to be significant and therefore were not included in the full covariate model.

The population PK model of GSK3640254 was integrated with the E-R model and short-term clinical trials simulations were conducted (500 trials with 60 participants/ dose level mrgsolve_0.8.9 package in R version 3.2.5) by sampling from the multivariate normal distribution and covariance matrix to include both uncertainty in parameter estimates and inter-subject variability. It was assumed that the bioavailability of GSK3640254 in Phase 2b will be similar to that from study 208132 (Phase 2a). For each individual, the anticipated response (maximum viral load decline) and percent of maximum effect was estimated. Simulations were then summarized by computing the median percent of maximum effect for each dose across the trials. The results of the simulations summarized in Table 4 indicate that doses ≥100 mg QD administered with food are predicted to result in a median percent of maximum effect at day 8 of at least 75%. In addition, a 300 mg QD dose is not predicted to provide a significant increase in predicted % of maximum effect compared to the 200 mg dose.

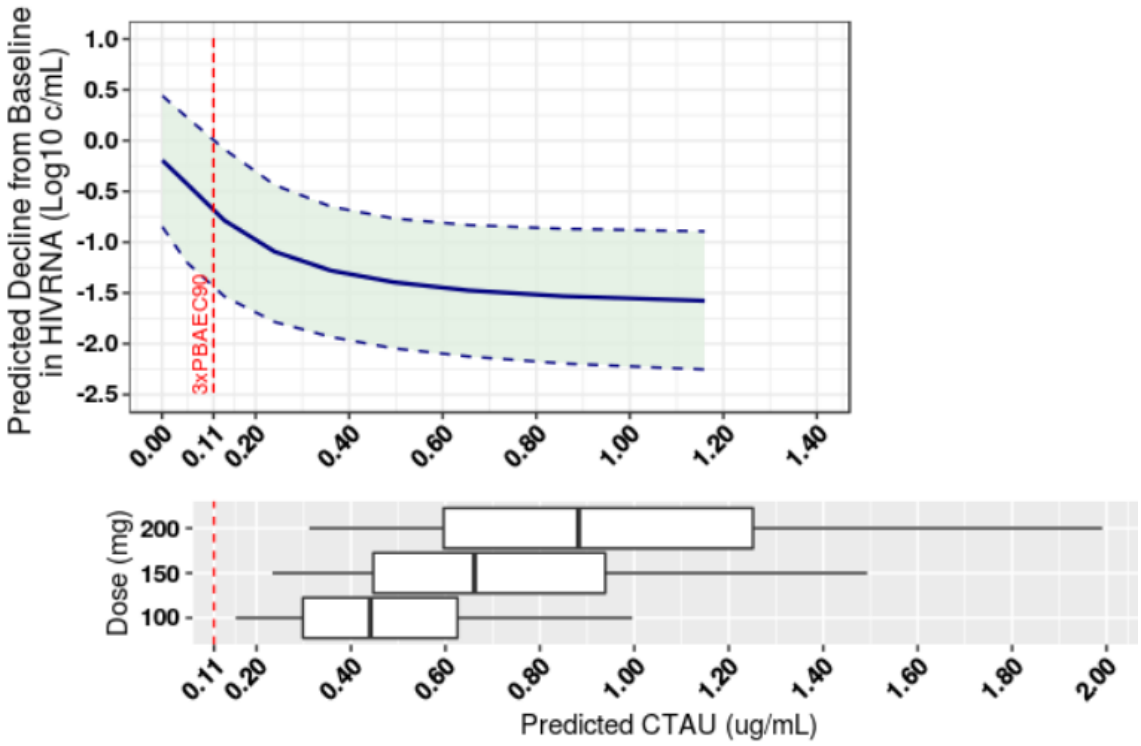
Table 4 Predicted Median Percent of Maximum Effect [90% PI] at Day 8 for GSK3640254 Doses Ranging from 75 mg to 300 mg QD administered with food (500 trials with n=60 participants per dose level)

Dose (mg)	Median [5%, 95%] Percent of Maximum Effect
75	70.4 [47.5, 95.4]
100	78.0 [54.5, 98.1]
125	83.1 [61.4, 99.6]
150	86.4 [66.6, 101]
200	90.4 [73.1, 102]
300	94.2 [80.1, 103]

PI = Prediction Interval

Figure 1 depicts the predicted decline in viral load versus Cτ at Day 8 and boxplot summary of predicted Cτ by proposed dose levels.

Figure 1 Simulated Predicted Decline in HIV-1 RNA versus Predicted Cτ at Day 8



Top panel – Dashed and solid blue lines are 5th, 95th and median of simulated data, respectively. Shaded area is the 90% prediction interval of simulated data. Bottom panel – the middle bar inside the boxes represents the median; the ends of the boxes are the 25th and 75th percentiles; the whiskers are the 5th and 95th percentiles of simulated Cτ. The red dashed line in both panels represents the 3xPBAEC90 (determined in-vitro based on virus with R361K/V362I/L363M substitutions).

Table 5 presents the model-predicted steady-state GSK3640254 PK parameters at the planned doses following QD administration with food. As expected, the predicted PK parameter values for the maximum proposed dose of 200 mg QD administered with food fall within the observed 95% CI of the geometric mean PK parameters from the PoC study 208132 (Table 3 in Section 2.2.4). The associated inhibitory quotient (IQ) for each dose was calculated by dividing Cτ median [5th – 95th percentiles] by the 3xPBAEC90 (Table 5).

The results show that all proposed doses are predicted to result in Cτ values >3xPBAEC90 in more than 95% of the participants (i.e. Cτ 5th percentile for the 100 mg dose >0.11 µg/mL) (Table 5). In addition, the planned doses provide a median IQ ranging from 4 – 8. Taking into account the variability in parameter estimates, the predicted IQ over the proposed doses ranges from 1.4 to 18.2. By comparison, for GSK3532795, a previous generation MI, the median IQ in phase 2b (calculated as Cτ/1xPBAEC90 based

on in-vitro Δ370 virus) for the 180 mg QD dose (maximum tested dose) was approximately 1.5. Therefore, assuming a biologically plausible correlate between Day 8 antiviral response and Week 24 efficacy, when GSK3640254 is combined with DTG, the response rate at week 24 is likely to be similar or better than GSK3532795 180 mg QD (i.e. >82.4% for week 24 snapshot HIV-1 RNA <40c/mL).

Table 5 Predicted Steady-State PK Parameters Median [90% PI] Following Once a Day Dosing of GSK3640254 with Food and Associated IQ

Dose (mg)	Median [5th – 95th Percentiles] [1]			
	Cmax (μg/mL)	AUC(0-24) (μg.h/mL)	Cτ (μg/mL)	IQ (Fold Above 3xPBAEC90)[2]
100	1.11 [0.652-1.9]	15 [8.2-27]	0.442 [0.153-0.999]	4 [1.4 - 9.1]
150	1.67 [0.978-2.85]	23 [12-41]	0.663 [0.23-1.5]	6 [2.1 - 13.6]
200	2.22 [1.3-3.8]	30 [16-54]	0.883 [0.307-2]	8 [2.8 - 18.2]

PI = Prediction Interval

[1]All simulations included uncertainty and inter-subject variability in parameter estimates.

[2] 3xPBAEC90 = 0.11 μg/mL based on in-vitro virus containing R361K/V362I/L363M substitutions.

Calculated Fold Coverage for Selected Doses

Predicted GSK3640254 safety coverage based on NOAEL and LOAEL exposure in the non-clinical chronic toxicity studies in rat and dog for the at the planned doses given once daily with food are presented in Table 6.

Table 6 Predicted Safety Cover Following Once a Day Dosing of GSK3640254 with Food

Dose (mg)	Fold cover dog NOAEL:human AUC(0-24) [1]	Fold cover rat LOAEL:human AUC(0-24) [2]	Fold cover dog LOAEL:human AUC(0-24)[3]
100	0.56	1.26	3.1
150	0.36	0.82	2.0
200	0.28	0.63	1.6

1 Based on dog NOAEL mean AUC of 8.37 from non-clinical chronic studies and the model-predicted median AUC (Table 5).

2 Based on rat LOAEL mean AUC of 18.9 μg.h/mL from non-clinical chronic studies and the model-predicted median AUC (Table 5).

3 Based on dog LOAEL mean AUC of 46.4 μg.h/mL from non-clinical chronic studies and the model-predicted median AUC (Table 5).

At the highest planned dose of 200 mg QD, the model-based predicted exposure corresponds to 0.3-fold the NOAEL (AUC = 8.37 ug.hr/mL) in dogs, 0.6-fold the LOAEL in rats (AUC = 18.9 ug.hr/mL) and 1.6-fold the LOAEL in dogs (AUC = 46.6 ug.hr/mL) from chronic toxicity studies (See Section 2.2.2). All microscopic findings in the stomach of rats and dogs and changes in serum gastrin were shown to be reversible. Potential effects in the stomach of humans during clinical trials are being investigated in a gastric substudy in study 208379, with appropriate clinical monitoring for GI intolerability in study 212483.

With regard to potential for QT prolongation, in the concentration-QTc analysis using the Multiple Ascending Dose data collected in the FTIH study 207187, a QTcF effect above 10 ms could be excluded up to GSK3640254 mean plasma concentrations of approximately 2000 ng/mL, which corresponds to doses of approximately 200 mg. As described in Section 2, there is a cardiovascular risk mitigation strategy for QT prolongation.

Evaluated and anticipated Drug Interactions Between GSK3640254 and DTG

In this Phase IIb study, GSK3640254 will be combined with DTG.

DDI risk with DTG

A Phase 1, two-way drug interaction study with GSK3640254 and DTG showed no effect on plasma GSK3640254 PK. GSK3640254 200 mg QD increased plasma DTG AUC(0-τ), Cmax and Cτ by 17%, 9%, and 24%, respectively. These increases were not considered clinically meaningful.

In summary, based on the lack of observed or predicted clinically meaningful drug interactions, GSK3640254 can be administered with DTG without dose adjustments.

Assessment of the Change in Formulation and Effect of Food

The recently completed Phase 2a clinical trial (208132) utilized capsules; this Phase 2b will use tablets. Study 213567 was a relative bioavailability and food effect study performed to compare the exposures between the GSK3640254 tablet and capsule in the presence of moderate fat meal and to investigate the effect of food on the PK of the GSK3640254 tablet. As shown in Table 7, the tablet provided similar exposures to the capsule when both were given with food.

Table 7 Assessment of Relative Bioavailability: Preliminary Statistical Comparison of Plasma GSK3640254 PK Parameters Based on Nominal Time (Study 213567)

PK Parameter	Ratio of GLS Means for Test vs. Reference [90%CI] (%Ref)
AUC(0-∞) h*μg/mL	99.8 [92.6, 108]
AUC(0-t) h*μg/mL	100 [93.2, 108]
Cmaxμg/mL	109 [98.8, 121]

1. Ref: Treatment A; Test: Treatment B

Treatment A: GSK3640254 200 mg (capsules) administered under moderate fat conditions.
Treatment B: GSK3640254 200 mg (tablets) administered under moderate fat conditions.

The summary of the statistical analysis for the assessment of food effect presented in Table 8 shows that GSK3640254 AUC(0-∞) and Cmax values following administration of the tablet with a moderate fat meal are 345% to 484% higher relative to administration in a fasted state, respectively. In addition, GSK3640254 AUC(0-∞) and Cmax following administration of the tablet with a high fat meal is 306% to 365% higher relative to administration in fasted state, respectively.

Table 8 Assessment of Food Effect: Preliminary Statistical Comparison of Plasma GSK3640254 PK Parameters Based on Nominal Time (Study 213567)

PK Parameter	Test vs Ref	Ratio of GLS Means for Test vs. Reference [90%CI] (%Ref)
AUC(0-∞) h*μg/mL	C vs D	345 [288, 413]
	E vs D	306 [256, 366]
AUC(0-t) h*μg/mL	C vs D	378 [318, 449]
	E vs D	335 [282, 399]
Cmaxμg/mL	C vs D	484 [391, 599]
	E vs D	365 [295, 451]

Treatment C: GSK3640254 200 mg (tablets) administered under moderate fat conditions (test).
Treatment D: GSK3640254 200 mg (tablets) administered under fasted conditions (ref).
Treatment E: GSK3640254 200 mg (tablets) administered under high fat conditions (test).

In summary, the results from the RBA and food effect study indicate that no dose adjustments are required due to the change in formulation based on:

- The similarity in PK parameters between the tablet to used in this Phase 2b study and the capsule used in the Phase 2a in the presence of a moderate fat meal.
- The dose predictions are based on modelling of the data from studies in which GSK3640254 was administered with food.

In conclusion, 212483 is anticipated to study a range of exposures which should provide therapeutic benefit (virologic suppression from antiviral activity) while being well tolerated in combination with DTG.

4.4. End of Study Definition

The end of the study is defined as the date of the last Week 52 visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all phases of the study up to and including the Week 52 visit.

5. STUDY POPULATION

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

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the ViiV Healthcare Investigational Product (IP) or other study treatment that may impact participant eligibility is provided in the current IB

GlaxoSmithKline Document Number 2018N379610_02 for GSK3640254, and in the current IB GlaxoSmithKline Document Number RM2007/00683/14 for DTG/3TC.

Participants are allowed to rescreen for this study one time with the exception of clinically irreversible findings in Screening; examples include but are not limited to: liver cirrhosis, CDC Stage 3 disease, drug allergy/sensitivity, significant psychiatric disorder, or cardiac arrythmias.

A single repeat test (retest) per laboratory analyte is allowed during a single Screening period to determine eligibility.

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Treatment-naïve, defined as no ARVs (in combination or monotherapy) received after a known diagnosis of HIV-1 infection

   NOTE: Use of PrEP (prior to known HIV-1 infection) is allowed and still meets inclusion. PrEP is used by individuals who are not infected with HIV-1 but who are at high risk for acquiring the virus. PrEP alone is not sufficient to treat HIV and the use of PrEP is stopped if/when a diagnosis of HIV is made.
3. Documented HIV infection and Screening plasma HIV-1 RNA ≥1000 c/mL;
4. Screening CD4+ T-cell count ≥250 cells/mm^3 .

Weight

5. Body weight ≥50.0 kg (110 lbs.) for men and ≥45.0 kg (99 lbs) for women and body mass index (BMI) > 18.5 kg/m^2. Calculations will utilize sex assigned at birth.

Sex

Sex and Contraceptive/Barrier Requirements

6. Male and female

a. **Participants who are male at birth**: There are no contraceptive requirements for participants who are male at birth
b. **Participants who are female at birth**:
   Contraceptive use by participants who are female at birth should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A participant who is female at birth is eligible to participate if they are not pregnant or breastfeeding, and one of the following conditions applies:
    - Is not a participant of childbearing potential (PONCBP) as defined in Section 10.4.

      OR

    - Is a POCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Section 10.4 during the study intervention period and until after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
        - If a hormonal method is selected, the participant is required to be clinically stable on it for at least one month prior to starting treatment in the study.
- A POCBP must have a negative highly sensitive serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 before starting study intervention.
    - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5 Pregnancy Testing.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy

Informed Consent

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

Other

8. **For participants enrolled in France:** a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

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

Medical Conditions

1. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy;

2. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia;

   Note: Other localized malignancies require agreement between the investigator and the Medical Monitor for inclusion.

3. Presence of primary HIV infection, evidenced by acute retroviral syndrome (e.g., fever, malaise, fatigue, etc) and/or evidence of recent (within 3 months) documented viremia without antibody production and/or evidence of recent (within 3 months) documented seroconversion;
4. Known history of liver cirrhosis with or without viral hepatitis co-infection;
5. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)
6. History of ongoing or clinically relevant hepatitis within the previous 6 months;
7. History of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation;
8. Any history of significant underlying psychiatric disorder, in the opinion of the Investigator or Medical Monitor, including but not limited to schizophrenia, bipolar disorder with or without psychotic symptoms, other psychotic disorders, or schizotypal (personality) disorder; or a clinical assessment of suicidality based on the responses on the eC-SSRS.
9. 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;

   Note: 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 Medical Monitor.

10. Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the Investigator or Medical Monitor (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;
11. A pre-existing condition, in the opinion of the Investigator or Medical Monitor, that could interfere with normal gastrointestinal anatomy or motility (e.g., gastroesophageal reflux disease [GERD], gastric ulcers, gastritis, inflammatory bowel disease), hepatic and/or renal function, or with the absorption, metabolism, and/or excretion of the study interventions or render the participant unable to take oral study treatment;

12. Myocardial infarction, acute coronary syndrome, unstable angina, stroke, transient ischemic attack, or intermittent claudication in the past 3 months;
13. Familial or personal history of long QT syndrome or sudden cardiac death;
14. Medical history, current or historical, of significant cardiac arrhythmias or ECG findings which, in the opinion of the Investigator or Medical Monitor, will interfere with the safety of the participant;

    Note: Examples of ECG findings include symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained ventricular tachycardia (VT) or sustained VT, second degree atrioventricular block (AVB) Mobitz Type II, or third degree AVB.

Prior/Concomitant Therapy

15. Active treatment for a viral infection other than HIV-1, such as Hepatitis B, with an agent that is active against HIV-1 (were known to be infected with HIV-1 after treatment for Hepatitis B was completed);
16. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening;
17. Treatment with any of the following agents within 28 days of Screening: radiation therapy, cytotoxic chemotherapeutic agents, any systemic immune suppressant;
18. Participants receiving any protocol-prohibited medication and who are unwilling or unable to switch to an alternate medication;
19. Participants who require concomitant medications known to be associated with a prolonged QTc (see list from https://www.crediblemeds.org).

Prior/Concurrent Clinical Study Experience

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. 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.

Diagnostic assessments

22. Historical evidence (prior to study screening period) of the presence of resistance-associated mutations gag A364V or A364A/V. Historical evidence of the presence of resistance to the integrase inhibitor class or to lamivudine.
23. Creatinine Clearance <50 mL/min;
24. ALT ≥ 3x ULN or ALT ≥ 2x ULN and total bilirubin ≥ 1.5x ULN (upper limit of normal)
25. Evidence of Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs) and reflex HBV DNA as follows:
    a. Participants positive for HBsAg are excluded;
    b. Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA on reflex testing are excluded

    Note: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded.

    See SRM for further details.
26. Positive Hepatitis C antibody test result at Screening AND positive on reflex to Hepatitis C RNA;

    Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained
27. Known or suspected active COVID-19 infection OR contact with an individual with known COVID-19, within 14 days of study enrollment (WHO definitions Section 10.11.5.2.1). Note, this study does not require a negative molecular test for SARS-CoV-2 for entry into the study.
28. Untreated syphilis infection [positive rapid plasma reagin (RPR) at Screening] without documentation of treatment.

    Note: Participants with a known syphilis infection can be Screened for the study no sooner than 14 days after the last dose of treatment for the syphilis infections. Participants who are assessed to have syphilis by the Screening tests can be treated within the Screening period, though the start of study treatment can be no sooner than 30 days after the last dose of treatment for the syphilis infection.
29. Presence of moderate-to-severe hepatic impairment (Class B or C) as determined by Child-Pugh classification (see Section 10.7);
30. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator or Medical Monitor, would preclude participation in the study of an investigational compound;
31. Urine Drug Screen positive (showing presence of): Amphetamines, Barbiturates, Cocaine, MDMA, or Phencyclidine, or non-prescribed opiates, oxycodone, benzodiazepines, methadone, methamphetamines or tricyclic antidepressants;

Notes:

If the urine drug screen shows the presence of opiates, oxycodone, benzodiazepines, methadone, methamphetamines or tricyclic antidepressants that are prescribed, the participant can be considered for the trial at the discretion of the Investigator recognizing at the time of enrolment: no studies on relevant drug interaction or GSK3640254 absorption-distribution-metabolism-elimination (ADME) will have been completed.

A positive result for THC is not exclusionary, though the PI should assess usage and only refer for the treatment phase those participants who seem appropriate for the trial, i.e., whose use of marijuana would not interfere with the participant's ability to comply with the required daily dosing schedule and protocol evaluations, or that might compromise the safety of the participant.

32. Any clinically relevant Grade 4 laboratory abnormality at Screen, including results for creatine phosphokinase (CPK), ALT, and lipid abnormalities that lack a compelling explanation from the Investigator;

    Note: Grade 4 CPK, ALT and lipid abnormalities that are explained by the Investigator, and with assent from the Medical Monitor, will not exclude the participant.

33. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 28 days;

34. Exposure to more than 4 new investigational drugs or vaccines (exclusive of a SARS-CoV-2 potential indication) within 12 months prior to the first dosing day;

35. ECG Heart Rate <50 bpm or >100 bpm, or QTcF >450 msec;

    Notes:

    - A heart rate of <50 or >110 is exclusionary and cannot be rechecked to determine eligibility.
    - A heart rate from 101 - 110 bpm can be rechecked by a single repeat ECG or by vitals within 30 minutes to verify eligibility.
    - The QT interval is corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually over-read by the Investigator. QTcF is used to determine eligibility and discontinuation for a participant in this study.
    - The Investigator's or Medical Monitor's over-read can supersede that of the machine at any time.

36. FOR PORTUGAL ONLY: HIV-2 infection (either determined by prior testing, medical history, or obtained locally during the Screening window)

Exclusion Criteria 37 and 38 FOR FRANCE ONLY:

37. Persons deprived of their liberty by a judicial or administrative decision;

38. Adults subject to legal protection or unable to express their consent will not be included in the study

Other Exclusions

To assess any potential impact on participant eligibility with regard to safety, the Investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study interventions.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Study intervention administration during the double-blind phase of the study should be with a low-fat meal. Thereafter, during the open-label phase, dose administration with GSK3640254 requires participants to take their dose with a low-fat meal (may include but not limited to 400-500 calories, with 25% calories from fat) [FDA, 2019].

5.3.2. Caffeine, Alcohol, and Tobacco

- It is suggested that alcohol consumption should be limited throughout study participation to the following: An average weekly intake of <14 drinks for participants assigned as male at birth or <7 drinks for participants assigned as females at birth. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
- Only clinically minor to moderate use (as determined by the PI) of tobacco products will be allowed during study participation.
- Participants should refrain from the use of marijuana.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 24 hours before each clinic visit to reduce the chances of seeing a high CPK result in the study lab results.
- See Section 10.9.5 for follow up assessments for elevated CPK.

5.3.4. Counsel regarding safe sex practices

All participants should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods and on the risk of HIV transmission to an uninfected partner.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened an additional time if, in the opinion of the Investigator, a current clinical outlook of the participant seems favorable for study inclusion (and if the participant never received study medication in this trial). Rescreened participants will be assigned a new participant number and will sign a new ICF(s).

As noted in Section 5, clinically irreversible findings found during screening would result in the individual not being screened a second time; examples include but are not limited to: liver cirrhosis, CDC Stage 3 disease, drug allergy or sensitivity, significant psychiatric disorder, cardiac arrythmias, or established, archived drug resistance.

6. STUDY INTERVENTION(S) 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 Intervention(s) Administered

	GSK3640254	GSK3640254 Placebo	DTG	3TC	3TC Placebo	3TC[a]
Intervention Name	GSK3640254	Placebo to match GSK3640254	Tivicay (The clinical label will state Dolutegravir 50mg to match the SPC)	3TC (The clinical label will state Lamivudine 300mg)	3TC Placebo (The clinical label will state Placebo to match Lamivudine 300mg)	3TC (The clinical label will state Lamivudine 300mg)
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Capsule	Capsule	Tablet
Unit Dose Strength(s)	25 mg, 100 mg	N/A	50mg	300mg	N/A	300mg
Dosage Level(s)	Variable depending on dose	Variable depending on dose	One tablet per day	One capsule per day	One capsule per day	One tablet per day
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Background	Comparator	Placebo	Comparator
IMP and NIMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and Labeling	32 tablets per HDPE bottle, labelled per country requirement	32 tablets per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement	32 capsules per HDPE bottle, labelled per country requirement	32 capsules per HDPE bottle, labelled per country requirement	30 tablets per HDPE bottle, labelled per country requirement

a. 3TC (Lamivudine 300mg) tablets for the Open Label phase will not be over-encapsulated, the existing commercial pack presentation (with a clinical label) will be supplied.

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.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK and ViiV Healthcare.
- IP accountability will be evaluated using pill counts. This assessment will be conducted during each clinic visit through study completion or early withdrawal. IP accountability records must be maintained throughout the course of the study.
- Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study will use an IVRS/IWRS.

- All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information & directions for the IWRS will be provided to each site
- Study interventions will be dispensed at the study visits summarized in the SOA.
- Returned study intervention should not be re-dispensed to any other participant.

To minimize bias, all treatment arms will be blinded to the research participants and all study personnel during the study through Week 24. The Sponsor study team will also remain blinded until the database lock for the Week 24 analysis.

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

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

For the first 24 weeks of the study a participant will be withdrawn if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

Additionally, there may be modifications to study arm recruitment and/or study arm continuation and/or design in 212483 based on the outcome of the 208379 IDMC review, the 208379 Week 24 primary endpoint, and the potential 212483 IDMC review. Further details on the implications of these three analyses on the experimental dosing arms of study 212483 are described in Section 4.1.

6.4. Study Intervention Compliance

- When participants are dosed at the site, the date and time of each dose administered in the clinic will be recorded in the source documents.
- When participants self-administer study intervention(s) at home, compliance with study interventions will be assessed by direct questioning and review of the diary card during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.
- A record of the number of study interventions dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

6.5. Dose Modification

No dose modifications are allowed in this protocol, including for a decline in Creatinine Clearance.

Additionally, there may be modifications to study arm recruitment and/or study arm continuation and/or design in 212483 based on the 208379 Week 24 primary endpoint, and the 212483 IDMC review. Further details on the implications of these two analyses on the experimental dosing arms of study 212483 are described in Section 4.1. These constitute changes among the three established experimental doses (not modifying the established experimental doses).

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

The investigator is responsible for ensuring that consideration has been given to the poststudy care of the participant's medical condition, whether or not ViiV is providing specific post-study treatment.

- To provide continued access to an investigational drug to participants deriving therapeutic benefit, participants who have successfully completed 52 weeks of treatment may be given the opportunity to continue to receive their study treatment. During the blinded randomized phase: that could be non-optimal GSK3640254 + DTG, optimal GSK3640254 + DTG, or 3TC + DTG).

- During the open label randomized phase:
  - Any participant who received 3TC + DTG beyond their individual Week 52 visit will discontinue from the study and be transferred to locally available standard of care treatment.
  - Any participant who received GSK3640254 + DTG beyond their individual Week 52 visit will be switched to a single optimal dose of GSK3640254 once it is determined from the ongoing Study 208379. After this occurs, participants who continue to receive GSK3640254 + DTG beyond their individualized Week 52 will have the option to continue on open label optimal dose GSK3640254 + DTG until either they or their healthcare provider decide to discontinue study treatment or until GSK3640254 + DTG is receives local marketing authorization and is commercially available).
- Continued access to GSK3640254 + DTG in Study 212483 may occur, as described above, provided all of the following conditions are met:
  - There is evidence of continued clinical benefit for the participant, and
  - There are no comparable alternative treatment options available, and
  - Such provision of GSK3640254 + DTG is permitted under local laws and regulations.

Continued access to an investigational drug will cease if the participant no longer derives clinical benefit from receipt of GSK3640254 + DTG; the participant meets a protocol-defined reason for discontinuation; or the development of GSK3640254 + DTG is discontinued.

Participants who meet the criteria outlined above and who consent to continued access to study treatment beyond their individual Week 52 will be required to attend continued access visits approximately every 12 weeks for safety and efficacy follow-up, as per the SOA (see Section 1.3). Should a participant with continued access discontinue study treatment for any reason, this should be reported to the Sponsor together with the reason for discontinuation.

6.7. Treatment of Overdose

Any tablet intake exceeding the randomized daily number of tablets will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 5 days).

3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the 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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines (e.g. Influenza vaccine or SARS-CoV-2 vaccine) may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn when possible. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment if possible.

DTG should be administered with the following considerations:

- 2 hours before or 6 hours after taking antacid or laxative products or sucralfate containing polyvalent cations (e.g. aluminium and magnesium) or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions.
- Concurrent administration with multivitamins is acceptable. Iron supplements can be taken with study treatment provided that all are taken together with a meal.
- Under fasted conditions, DTG should be given 2 hours prior to OR 6 hours after iron supplements.

Metformin concentrations may be increased by DTG. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG with metformin, to maintain glycemic control.

Clinical monitoring is recommended for participants taking methadone, as methadone maintenance therapy may need to be adjusted in some participants.

Non-protocol defined treatments or medical interventions (e.g., physical therapy, radiotherapy, surgical procedures) are permitted during the study for appropriate medical management of the participant.

6.8.1. Prohibited Medications and Non-Drug Therapies

6.8.1.1. Prohibited Medications: All Participants

The following, general concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents (which do not have emergency, conditional, or standard market authorization), antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered. Approval for potential co-enrolment of a study participant in a study not involving an experimental agent (e.g., a questionnaire, research method, health monitoring etc), must be obtained from the Sponsor before co-enrolment).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SRM) This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used if a participant has an acute viral hepatitis [James, 2009].

6.8.1.2. Medications that need to be stopped in Screening

The following medications need to be stopped at least 4 weeks prior to the first dose:

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine
- St. John's wort (*Hypericum perforatum*)
- Any other strong CYP3A Inducers (e.g., dexamethasone, rifapentine, rifabutine, etc)
- Fampridine

The following medications need to be stopped at least 2 weeks prior to the first dose:

- Dofetilide and pilsicainide
- Any substrate of organic cation transporter 2 (OCT2), with a narrow therapeutic window should not be administered concurrently with DTG containing products (see prescribing information [TIVICAY, 2020 and DOVATO, 2020]).

6.8.1.3. On Treatment Prohibited Medications: GSK3640254

The following medications may significantly interact with GSK3640254 and are not permitted during the double-blind phase and thereafter not permitted with GSK3640254:

- Strong CYP3A inhibitor (Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole etc);
- Strong CYP3A inducer (e.g. phenobarbital, dexamethasone, carbamazepine, phenytoin, rifampin, rifapentine, rifabutine, St John's wort, etc);
- Substrate of OATP1B3 (e.g. telmisartan, valsartan, olmesartan, rifampin, ezetimibe, statins such as atorvastatin, rosuvastatin, pitavastatin).

6.8.1.4. On Treatment Prohibited Medications: When dosing with DTG in any arm

- The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, they may not be administered concurrently in participants on the DTG arm.
  - Carbamazepine
  - Oxcarbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifampicin and rifapentine
  - St. John's wort (*Hypericum perforatum*)
  - Fampridine
- Dofetilide and pilsicainide are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.
- Any substrate of organic cation transporter 2 (OCT2), with a narrow therapeutic window should not be administered concurrently with DTG containing products (see prescribing information [TIVICAY, 2020 and DOVATO, 2020]).

For information on concurrent therapies and interactions suspected to be relevant to 3TC, please consult the local prescribing information.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Upon study discontinuation, cART should be started, as selected/prescribed/provided by their physician.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will perform an early withdrawal visit. See the SOA 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.

Participants must be discontinued from the study for any of the following reasons:

- Confirmed or Suspected Hypersensitivity Reaction;
- Confirmed Virologic Failures as defined in Section 7.1.1;
- Virologic Non-Responder at Week 24, defined as participants who have either:
  - HIV-1 RNA ≥200 c/mL at Week 24, or
  - HIV-1 RNA ≥50 c/mL on repeat testing of Week 24 results and prior to Week 28 (see Figure 2);
- Participant requires substitution or dose modification of GSK3640254, DTG or 3TC;
- Treatment emergent resistance to any component of the study medications. For participants receiving GSK3640254, the genotypic emergence of an A364V or A364A/V requires discontinuation;
- For participants receiving GSK3640254, a PhenoSense Gag $cFCIC_{50} > 50$ (on-treatment [CCI] Day 1 [CCI];
- Liver toxicity where stopping criteria specified in Section 7.1.2 are met;
- Allergic reaction or Rash criteria as described in Section 10.9.2 and Section 10.9.3, respectively, are met and no compelling alternate cause is identified;
- Renal toxicity is met and no compelling alternate cause is identified (an estimated GFR of <50 mL/min on confirmed measurement as defined in Section 10.9.6);
- Confirmed Proximal Renal Tubule Dysfunction (PRTD) (See Section 10.9.7);
- Pregnancy (intrauterine), regardless of termination status of pregnancy (See Section 8.2.5);
- Diagnosis of Hepatitis B or C viral infection;
- Any clinically significant AE deemed to require discontinuation of the IP;

- Moderate to severe (as clinically determined by the investigator) COVID-19 infection (suspect, probable, or confirmed using the most recent version of the WHO case definition);
- A Grade 4 or related Grade 3 AE: the Investigator will discontinue the participant from the study. If the AE, in the opinion of the investigator, may be representative of gastric toxicity (e.g. obstipation, diarrhea, dysphagia/odynophagia, GI bleeding, mucositis/stomatitis, or nausea), the Investigator may consider performing an evaluation/management plan incorporating elements in the GI Intolerability Evaluation and Management table (See Section 8.2.7);
- Any Grade 3 or higher Psychiatric AE. The Investigator will discontinue the participant from the study and arrange for emergency psychiatric evaluation/management; the panel for drugs of abuse will be tested;
- New onset suicidal ideation, as clinically diagnosed by the Investigator (in consultation with psychiatry, if needed). The Investigator will discontinue the participant from the study and arrange for urgent specialist psychiatric evaluation/management;
- CCI [redacted]
- Participants who require concomitant medications known to be associated with a prolonged QTc;
- A triplicate set of on-treatment ECGs show the average QTcF >500 msec or increase from baseline QTcF >60 msec (See Section 7.1.3).

7.1.1. Protocol-Defined Virologic Failure

Virologic failure must be confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between two and four weeks after the initial suspected virologic failure sample.

Participants should receive full dose of study treatments across all plasma sampling times used for determining virologic failure.

For the purposes of clinical management in this study, protocol-defined virologic failure (PDVF) is defined as any of the following:

Virologic Non-response

- Decrease from Baseline (Day 1) in plasma HIV-1 RNA of <1.0 log10 c/mL unless plasma HIV-1 RNA is <200 c/mL by Week 12;
- Confirmed plasma HIV-1 RNA levels ≥200 c/mL at or after Week 24 (See Figure 2 and Table 9);
- Plasma HIV-1 RNA ≥50 c/mL on repeat testing of Week 24 results and prior to Week 28 (see Figure 2).

Virologic Rebound

- Confirmed plasma HIV-1 RNA ≥200 c/mL after confirmed consecutive plasma HIV-1 RNA <50 c/mL (see Table 9).

Participants who meet the definition of virologic failure must be immediately discontinued from the study.

7.1.1.1. Managing Suspected Virologic Failure/Endpoint Cases

Inadequate adherence is a common cause for virologic failure and should be explored as a first step in management of study participants (e.g., at the first indication of inadequate virologic response or rebound).

All cases that meet a criterion for suspected virologic failure must be confirmed by a second measurement performed at least 2 weeks but not more than 4 weeks (as specified below) apart from the date of the original sample, unless one of the extenuating circumstances outlined below applies.

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as a suspected virologic failure, the Investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of therapy.

The following guidelines should be followed for scheduling confirmatory plasma HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to <4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all IP.
- Confirmatory testing should be scheduled 2 to <4 weeks following any immunization, during which time the participant should receive full dose(s) of all IP.
- If therapy is interrupted due to non-compliance, or other reasons, confirmatory testing should be scheduled 2 to <4 weeks following resumption of full dose of all IP.
- The participant should have received full doses of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

Sites should contact the study medical monitor to discuss individual participants, whenever necessary.

7.1.1.2. Managing Confirmed Virologic Failure/Endpoint Cases

A participant who meets confirmed virologic failure must be immediately discontinued from the study. Once a participant has been confirmed as meeting the protocol definition of confirmed virologic failure, a sample from the suspected virologic failure visit, and a sample from the Day 1 visit (if not sent previously), will be sent for genotypic and phenotypic resistance testing and the result made known to the Investigator when available.

If the confirmed HIV-1 RNA level is ≥50 and <200 c/mL, and the decision is taken to withdraw the participant, resistance testing will not be done and the participant should be transitioned off study intervention immediately. For all other confirmed virologic failure cases where HIV-1 RNA ≥200 resistance testing will be triggered.

If a participant is withdrawn early from participation in the study, the Investigator must make every effort to perform the evaluations outlined in the Schedule of Activities. These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any participant from the study.

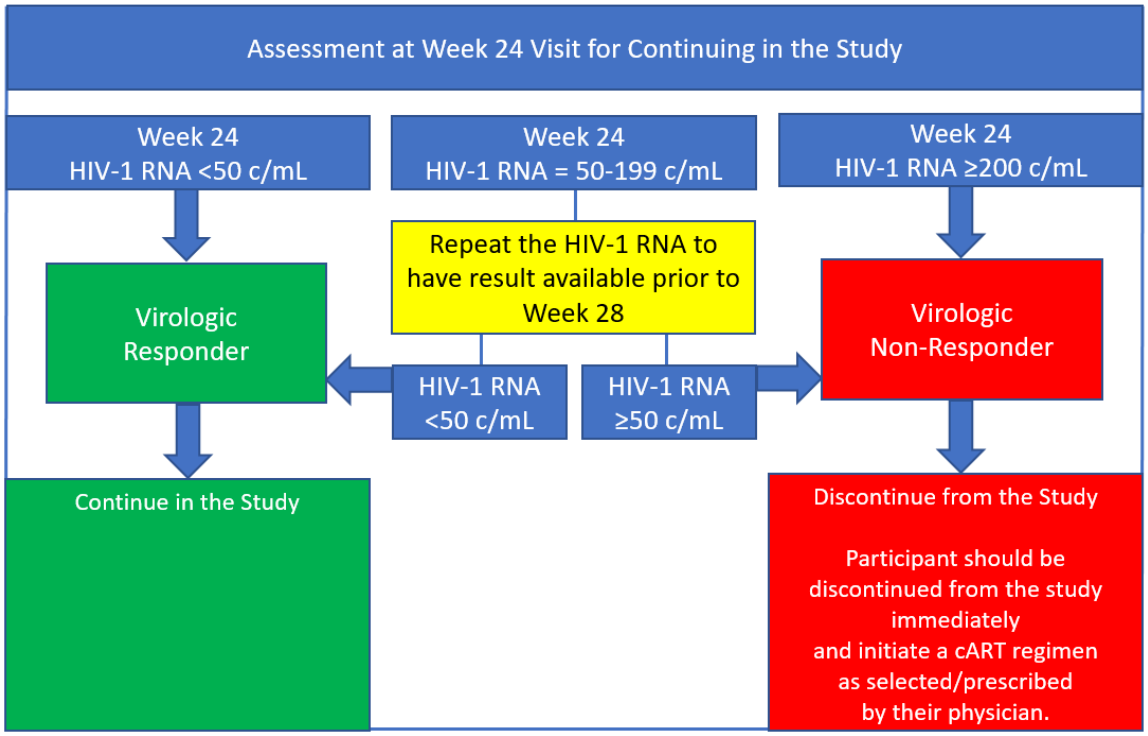
7.1.1.3. Virologic Management

See the decision tree in Figure 2.

Participants in any arm who are Virologic Responders (HIV-1 RNA <50 c/mL) within the Week 24 Snapshot Window will continue in the study beyond Week 24.

Participants in any arm who are Virologic Non-Responders (HIV-1 RNA ≥ 50 c/mL on confirmatory testing as shown in the Figure below) must be discontinued from the study immediately. These participants will perform the Early Withdrawal visit, and then be seen in clinic once more at a Final Follow-Up visit if needed.

Figure 2 Assessment by HIV-1 RNA at Week 24



Refer to Table 9 for management by HIV-1 RNA after Week 24.

For the purposes of clinical management in this study, Investigators will continuously assess HIV-1 RNA throughout the Treatment Phase of the trial (from Day 1, at any visit either scheduled or unscheduled) using information found in this section and in Table 9 (after Week 24).

Table 9 Assessment by HIV-1 RNA after Week 24

Current HIV-1 RNA <50 c/mL	Regardless of previous HIV-1 RNA result, proceed with the next visit, per SOA in Section 1.3.
Current HIV-1 RNA ≥50 c/mL but <200 c/mL	If previous HIV-1 RNA result was <50 c/mL, perform a scheduled or unscheduled visit to reassess HIV-1 RNA[a] in a time frame consistent with Section 7.1.1. If previous HIV-1 RNA result was ≥50 c/mL, discuss results with the ViiV medical monitor[b,c] Participant has met criteria for additional HIV-1 RNA testing or possible withdrawal. If the participant is withdrawn under the above criteria, they will have met "Precautionary Virologic Withdrawal Criteria (PVW)" If the 2 previous consecutive HIV-1 RNA results were ≥50 c/mL and <200 c/mL, the participant has not met PVW.

Current HIV-1 RNA ≥200 c/mL	If previous HIV-1 RNA result was <50 c/mL, perform a scheduled or unscheduled visit to reassess HIV-1 RNA[a] in a time frame consistent with Section 7.1.1. Participant has met "Suspected Virologic Withdrawal Criteria (SVW)". • If the repeat HIV-1 RNA is ≥ 200 c/mL, the participant has met PDVF criteria[d] • If the repeat HIV-1 RNA is 50-199 c/mL, then discuss results with the ViiV medical monitor. If previous HIV-1 RNA result was ≥50 c/mL, the participant has met PDVF criteria[d]

a. Investigators should not schedule reassessment blood draws in the presence of factors that could be associated with virologic blips, such as intercurrent infection, treatment interruption due to toxicity management or non-compliance, or vaccination. Participants should have received full doses of study intervention for at least 2 weeks at the time of plasma HIV-1 RNA reassessment.
b. In case of withdrawal, a sample from the initial visit will be used for resistance testing. If resistance testing will not be done, withdrawing participants should be transitioned off study intervention as soon as possible.
c. The medical monitor and investigator should consider intercurrent illness, recent immunization, interruption of therapy or other non-virologic reasons associated with transient elevated HIV-1 RNA measurements ≥50 and <200 c/mL. If no non-virologic reasons are identified to explain the lack of virologic suppression, the participant must be withdrawn. If the Investigator and the medical monitor agree that the participant is experiencing a slow re-suppression due to one of the above issues, then a retest HIV-1 RNA measurement is required in in a time frame consistent with Section 7.1.1 . If the HIV-1 RNA remains ≥50 c/mL on a second retest (the third consecutive HIV-1 RNA assessment), the participant must be withdrawn.
d. Participants with confirmed HIV-1 RNA results in the range ≥200 c/mL to <500 c/mL, should be transitioned off study intervention and withdrawn from study immediately

7.1.2. 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). Refer to Appendix 6 in Section 10.6.

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

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.
- Liver Safety Required Actions and Follow up Assessments Section can be found in Section 10.6.

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

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

7.1.3. Columbia-Suicide Severity Rating Scale

Emergence of any positive (abnormal) response on the C-SSRS, confirmed by the Investigator, during the treatment phase of the study will be cause for immediate clinical assessment of suicidality (by the Investigator or a consulting psychiatrist). Emergence of new onset suicidal ideation or a Grade 3 or higher psychiatric AE will result in immediate discontinuation and urgent specialist psychiatric evaluation and management.

7.1.4. QTc Stopping Criteria

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

The Baseline QTcF should be based on averaged QTcF values of triplicate ECGs obtained over a brief recording period from the Day 1 pre-dose ECG (see Section 8.2.3).

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 can continue in the study 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 as an AE. The Investigator's or Medical Monitor's over-read can supersede that of the machine at any time. If so, it must be noted in the chart.

A randomized participant that develops an on-treatment single ECG QTcF >500 msec or an increase from baseline QTcF >60 msec should have two repeat unscheduled ECG's within 10 minutes apart. Using these three ECGs, if the average QTcF shows either of the following, the participant will be withdrawn from the study:

- >500 msec, or
- An increase from baseline QTcF >60 msec

- ViiV Healthcare encourages PI's to consult with a local cardiologist for assistance in interpretation of an EKG showing a prolonged QTcF (> 500 msec or increase > 60 msec). Finally, this participant should have 1) a complete, unscheduled chemistry panel, 2) an unscheduled GSK3640254 PK sample, and 3) repeated unscheduled ECGs until their QTc measurement returns to their original averaged QTcF value at Day 1 pre-dose.

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

7.1.5. Temporary Discontinuation

Participants may not have any temporary interruptions to their study intervention. Withdrawal of study intervention requires withdrawal from study.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation/withdrawal visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed, followed by the Study Completion eCRF for the Intervention Period.
- An early discontinuation/withdrawal visit should also be conducted if a participant who has been entered into the Continued Access Phase discontinues or is withdrawn from study treatment. The reason will be captured on a separate Continued Access Phase-related Completion eCRF page – different to that for discontinuation from the main study.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel (with the exception of HIV-1 resistance assays)
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

- Plasma for quantitative HIV-1 RNA will be generated at time points listed in the SOA (see Section 1.3).
- An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 40 c/mL will be used. However, the primary and secondary endpoints will define responders as HIV-1 RNA <50 c/mL.
- Details concerning the handling, labeling and shipping of these samples will be supplied separately.

8.1.1. Lymphocyte Subsets by Flow Cytometry

- Blood samples will be obtained from each participant for the analysis of lymphocyte subsets (CD4 and CD8) by flow cytometry at the timepoints listed in the SOA (Section 1.3).
- Details concerning the handling, labeling and shipping of these samples will be supplied separately.

8.1.2. Disease Progression

- HIV-associated conditions will be recorded as per the SoA (Section 1.3).
- CDC-classification will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (See Section 10.10).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A targeted physical examination will include, at a minimum, assessments of the skin, lungs, heart, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Investigators should pay special attention to any signs of rash.
- Height and weight will also be measured and recorded. Height will be captured only at Screening; Weight will be captured at each visit to accurately calculate Creatinine Clearance (CrCL) and also allow for careful monitoring of weight throughout the study. For guidance on weight measurement see Section 8.2.1.1.

8.2.1.1. Weight Measurement

Adapted from WHO STEPS Surveillance Manual [WHO, 2017].

Equipment

To measure weight, you will need a weighing scale, (such as a SECA scale or the Tanita HS301 Solar Scale). Alternatively, a BMI scale measuring both height and weight (e. g. Growth Management Scale) can be used.

Ensure the scale has been regularly calibrated according to the manufacturer instructions and that calibration documentations are filed and available to the study CRA as required.

We recommend using the same scale across visits for individual study participants.

We recommend having the same study staff performing the measurement across visits for individual study participants.

We recommend that the time of day a participant's weight is measured is consistent for every participant at the site within the study. (ex. If measured at 10 a.m. at initial measurement, attempt to have the participant measured at 10 a.m. at subsequent visits).

Set up requirements

Make sure the scales are placed on a firm, flat surface. Do not place the scales on:

- carpet
- a sloping surface
- a rough, uneven surface.

Set up scales

Follow the steps below before measuring the weight of a participant:

1. Make sure the scale is on a firm, flat surface.
2. Turn on the scale and wait until the display shows 0.0.

Procedures

Follow the steps below to measure the weight of a participant:

1. Ask the participant to remove their footwear (shoes, slippers, sandals, etc). They should also take off any heavy belts and remove all objects out of their pockets (example: mobile phones, wallets, coins).
2. Ask the participant to step onto scale with one foot on each side of the scale.
3. Ask the participant to:

- stand still
- face forward
- place arms on the side and
- wait until asked to step off.

4. Record the weight in **kilograms to one decimal place** in the eCRF.

8.2.2. Vital Signs

- Vital signs will be collected as indicated in the SOA (Section 1.3).
- Vital signs will be measured in a semi-supine position after 5 minutes rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and will include temperature, pulse rate (heart rate), respiratory rate, and systolic and diastolic blood pressure.
    - Blood pressure and pulse measurements will be done with a completely automated device. Manual techniques will be used only if an automated device is not available.
    - Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be recorded in the eCRF where the average of the 2 readings will be calculated.

8.2.3. Cardiac Monitoring with Electrocardiograms

- See Table 11 in Section 8.4.
- Triplicate and Single 12-lead ECGs will be obtained as outlined in the SOA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.3 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- Participant should remain still while the tracing is being recorded. Site staff should review the tracing to look for movement artefact and redo the ECG, if necessary.
- The high-quality ECG should be transmitted to the central vendor. If there is an issue with electronic transmission (via analog or LAN), sites will upload the ECG tracing to a site for vendor access.
- The central vendor will not be providing over-reads on any of the ECGs. The Investigator (or designee) should review the Screening output to determine if any exclusion criteria have been met. Subsequent ECGs should be assessed by the Investigator (or designee) for any new issue or parameter results that meet QTcF stopping criteria (See Section 7.1.3). In addition, review of such an ECG with a Cardiologist is encouraged.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 in Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. All protocol required laboratory assessments must be performed by central laboratory services. Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic. Laboratory assessments must be conducted in accordance with the Laboratory Manual, and SoA (Section 1.3). Details for the preparation and shipment of samples will be provided by PPD central lab and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by PPD central lab.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification) the results must be recorded in the eCRF. Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.
- See Section 10.2 for the list of clinical laboratory tests to be performed and Section 1.3 for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, 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 should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- Refer to the SRM for processing and handling of samples to avoid duplicate and/or additional blood draws.

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Participants of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 to be eligible for the start of administration of IP.
- Pregnancy testing (urine and/or serum as required by local regulations) will be conducted at Screening, Day 1, and at monthly intervals during study intervention period, as outlined in the SOA (Section 1.3).

8.2.6. Suicidal Ideation and Behaviour Risk Monitoring

The reason for the use of the electronic version of the Columbia Suicidality Severity Rating Scale (eC-SSRS) assessment in this study is two-fold:

1. Participants with HIV infection occasionally may present with symptoms of depression and/or other relevant psychiatric diagnoses that increase the risk for suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some participants being treated with INIs, including DTG.
2. GSK3640254 is not a CNS active drug nor is it being developed for a neurologic or psychiatric condition. However, the risk of suicidal ideation was identified with the previous generation MI GSK3532795 at supratherapeutic doses.

Therefore, the use of the eC-SSRS is appropriate to monitor participants for potential risk of suicidality before and during treatment. At the Screening visit, participants will

complete the baseline eC-SSRS lifetime assessment. At all other visits, participants will complete the eC-SSRS based on changes from the last visit. Participants can complete the eC-SSRS ±7 days from each visit post-randomization.

Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour (SIB) or any other unusual changes in behaviour. It is recommended that the investigator promptly refer participants for psychiatric evaluation and management who experience signs of SIB if encountered during the screening period.

If randomized and on-treatment, participants presenting with new onset/treatment emergent depression (e.g. Grade 3-4) should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop because discontinuation of study medication and urgent specialist psychiatric evaluation and management are required. Independent of psychiatric symptoms, an on-treatment eC-SSRS will be performed at all study visits. Ultimately, in the event of a new onset suicidality as clinically diagnosed by the Investigator (in consultation with psychiatry, if needed), the participant will discontinue from the trial and the PI will arrange for urgent specialist psychiatric evaluation and management.

Assessment of treatment-emergent suicidality will be clinically diagnosed but monitored during this study using the eC-SSRS. The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months); all subsequent questioning is in relation to the last assessment.

- Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to GSK/ViiV Healthcare/Syneos Health within 1 week of the investigator diagnosing a possible suicidality-related AE.
- In addition to new onset suicidality, emergent non-suicidal Psychiatric AEs will be evaluated and managed in the following manner:
- **Any Grade 1 or 2 Psychiatric AE:** A Grade 1 or 2 Psychiatric AE may result in additional unscheduled visits (in-clinic or at home) as clinically indicated. This may include a more in-depth assessment of AE through interview, additional unscheduled clinical labs, and/or imaging. Psychiatric consultation may be required at the discretion of the PI. Any pharmacotherapy should be discussed with the Medical Monitor.

- **Any Grade 3 or 4 Psychiatric AE:** As described in Section 7.1, a Grade 3 or 4 Psychiatric AE will result in discontinuation from the trial and emergency psychiatric evaluation. A urine sample should be submitted for the Drugs of Abuse panel.

8.2.7. GI Intolerability Evaluation & Monitoring Plan (with Stopping Criteria)

Pre-clinical toxicology studies in rats and dogs have suggested a potential for GI related toxicity with GSK3640254. Prior clinical trials have not evaluated for the presence of gastric toxicity in humans. Thus, it is unclear if any of the GI AEs observed in any clinical trial were representative of, associated with, or resulted from gastric toxicity (if present). Thus, in a clinically conservative fashion, this section provides general guidance to the Investigator on the evaluation and management of primarily upper gastrointestinal symptoms (Table 10). The Investigator may contact the Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the trial.

Table 10 GI Intolerability Evaluation and Management

HISTORY	**For symptoms of all grades, a thorough history (and differentiation of acute and chronic manifestations) forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical trial.**
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].

HISTORY	**For symptoms of all grades, a thorough history (and differentiation of acute and chronic manifestations) forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical trial.**
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 trial are available. [Stanghellini, 2016 and Lacy, 2016]
PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history [Hasler, 2012]. The exam 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.**

HISTORY	**For symptoms of all grades, a thorough history (and differentiation of acute and chronic manifestations) forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical trial.**
DIAGNOSTIC EVALUATION AND MANAGEMENT	**A major goal in the diagnostic evaluation of a participant with upper GI symptoms is to quickly arrive at a final diagnosis without exposing the participant to unnecessary (invasive) testing; Investigators should exercise good clinical judgment in this regard [Soll, 2009]. A major goal of therapy is directed at correcting the underlying identifiable medical or surgical abnormalities (e.g perforation or infarction) [Malagelada, 2016]. Consultation (e.g., gastroenterologist) is recommended as clinically indicated. Emergent action should be taken as necessary: correction of hypovolemia or electrolyte abnormalities.**
Grade 1 symptoms	Participants may be treated symptomatically. If participants develop dyspepsia alone, generally only limited and direct diagnostic testing should be performed. If the participant has dyspepsia, they should limit alcohol, caffeine, chocolate, tobacco, and eating directly before bedtime.
Grade 2 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): Serum chemistries (for evaluation of fluid and acid/base/metabolic status) and assessment of white blood cells (with differential) and hemoglobin if not recently performed. Amylase and Lipase may also be appropriate. Polymerase chain reaction (PCR) for viruses (e.g., Cytomegalovirus [CMV])

HISTORY	For symptoms of all grades, a thorough history (and differentiation of acute and chronic manifestations) forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical trial.
Grade 3 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • CT scan to identify gastrointestinal inflammation • Upper endoscopy with biopsy as indicated (eg, mucosal injury or the presence of red flags). Generally, use of imaging should be appropriate and timely. Management should be targeted at addressing the underlying pathology.
Grade 4 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 and Grade 3 • An acute abdominal series • Focused Assessment with Sonography in Trauma (FAST) Ultrasound Initial management can include correction of hemodynamic and electrolyte abnormalities as clinically indicated. After stabilization, management should be targeted at addressing the underlying pathology.

[a] Grade 4 or related Grade 3 AE: The Investigator will discontinue the participant from the study (see Section 7.1). If the AE, in the opinion of the investigator, may be representative of gastric toxicity (e.g. obstipation, diarrhea, dysphagia/odynophagia, GI bleeding, mucositis/stomatitis, or nausea), the Investigator may consider performing an evaluation/management plan incorporating elements of the above GI Intolerability Evaluation and Management table.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the follow-up visit 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/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 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in participants will be collected after the start of study intervention and until 35 days after the last dose. Details of pregnancies in partners of participants do not need to be collected in this study.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK/ViiV Healthcare/Syneos Health within 24 hours of learning of the female participant 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 will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to GSK/ViiV Healthcare/Syneos Health.
- GSK's central safety department will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers and licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.
- 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, he or she may learn of an SAE through spontaneous reporting.

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

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 , Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes (HIV-Associated Conditions)

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.10) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (Section 10.3.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If any of the above conditions is met then record the Disease Related Event on either the AE or SAE page (according to severity) in addition to the HIV Associated Conditions eCRF page. If it is categorized as an SAE, report promptly (Section 10.3.5) to GSK/ViiV Healthcare/Syneos Health.

Additionally, the PI should designate on the eCRF whether or not the AE or SAE meets any aspect of being an AIDS defining condition.

8.3.8. Adverse Events of Special Interest

- AEs of special interest (AESIs) include those related to GI intolerability/gastric toxicity, neuropsychiatric safety, QT prolongation and skin and subcutaneous disorders. See Section 8.2.3, Section 8.2.6, Section 8.2.7 and Section 10.9.3 for further details.

8.4. Pharmacokinetics

All participants will provide samples for PK analysis.

Participants will be expected to complete a dosing card with the date and time of IP administration of the last three doses prior to the scheduled clinic visits at which PK is collected (Weeks 2, 4, 8, 12, 24, and 48). These dates and times will be recorded in the eCRF. Additionally, dosing information on the clinic day, including whether or not the dose was administered with food, and the actual date and time of the PK samples must be recorded in the eCRF.

The pre-dose samples **must** be collected within the window of 20-28 hours after the most recent dose taken.

- Blood samples will be collected for measurement of plasma concentrations (including but not limited to GSK3640254) at the visits outlined in the SoA and as detailed in Table 11).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Genetic analyses will not be performed on these plasma samples.
- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Table 11 Pharmacokinetic Sampling Schedule, Cardiac Monitoring with ECGs and Related Activities

	Time (Event)	Window for blood draw	Time (Relative to Dosing) Hour: Min
	Morning pre-dose work:		

	Time (Event)	**Window for blood draw**	**Time (Relative to Dosing) Hour: Min**
Week 2 (Days 11-14)	20-28 hrs after the dose was taken the day prior: ECGs, vitals and full blood draw (including the pre-dose PK collection)[a]		
	Eat Meal **DOSE**[b]**:** Administer study treatment and start the clock.		00:00
	2 hr ECG		02:00
	4 hr ECG		04:00
	6 hr ECG		06:00
Week 4	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection)[a]		
	Eat meal. Administer dose[b]		00:00
Week 8	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection)[a]		00:00
	Eat meal. Administer dose[b]		00:00
Week 12	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection)[a]		
	Eat meal. Administer dose[b]		00:00
	ECG 2-6 hrs post dose		02:00 - 06:00
	1 PK blood sample 2-6 hours post-dose[c]	± 15 minutes	02:00 - 06:00
Week 24	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection).[a]		
	Eat meal. Administer dose[b]		00:00
	ECG 2-6 hrs post dose		02:00 - 06:00

	Time (Event)	**Window for blood draw**	**Time (Relative to Dosing) Hour: Min**
	1 PK blood sample 2-6 hours post-dose[c]	± 15 minutes	02:00 - 06:00
Week 48	20-28 hrs after the dose was taken the day prior: Draw lab kit (including the pre-dose PK collection).		
	Eat meal. Administer dose[b]		00:00
	ECG 2-6 hrs post dose		02:00 - 06:00

a) The pre-dose, full morning blood draw and ECG should be done in the standard required sequence of assessments: ECG – Vitals – Blood Draw (all within 15 minutes to ensure that the PK sample from the blood draw approximates that of the ECG).
b) At visits with PK collections, aim to dose the participant near the same time that they have typically been dosing. Best Practice is to plan for approximately 30-45 minutes in which to get these pre-dose assessments and procedures done and the meal consumed by the participant.
c) Each post-dose blood draw should be drawn relative to the time the dose was given; never base the interval for the next blood draw on the time of the previous blood draw

8.5. Genetics and/or Pharmacogenomics

A 6 mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected on Day 1 (or at any time later) from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to take part in the genetic research may still participate in the main study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual and the SRM.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.6.1. Viral Genotyping and Phenotyping Analyses

Some of the plasma samples collected in this study will be used to test for the incidence of treatment emergent genotypic and phenotypic resistance to reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors and the study intervention, GSK3640254 maturation inhibitor.

- Development of virologic failure in any participant will trigger shipment for resistance testing of the sample collected at the time point of interest, accompanied by the Day 1 sample for the same following 5 assays: PhenoSense GT, GeneSeq Integrase, PhenoSense Integrase, PhenoSense Gag assays for GSK3640254, and Gag genotype (using a Next Generation Sequencing platform).

The resistance assays will be performed at Monogram Biosciences.

Details of the analyses to be performed will be specified in the SAP.

8.7. Immunogenicity Assessments

Not Applicable.

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

The study is designed to investigate the efficacy, safety, tolerability and resistance of three doses (100 mg, 150 mg, and 200 mg) of GSK3640254 + DTG, relative to DTG + 3TC for 24 weeks. Although no formal statistical analysis will be carried out in this study, Bayesian analyses will still be conducted to evaluate the probability that the Week 24 response rate, defined as the proportion of participants with plasma HIV-1 RNA <50 c/mL as calculated by the FDA snapshot algorithm, of the optimal dose of GSK3640254 has comparable efficacy to the reference treatment using a 12% margin. A positive sign of efficacy will be achieved if any GSK3640254 dose has a high posterior probability (e.g., ≥75%) of being within the 12% margin.

The effectiveness of the components of DTG + 3TC have been assessed in numerous previous studies with DTG + 3TC, including GEMINI-1 and GEMINI-2. Historical data from these studies suggests that the Week 24 response rate for treatment naïve participants treated with DTG + 3TC is 90~92%. In Bayesian model of the final analysis, the noninformative prior Beta (1,1) will be utilized for the reference arm to calculate the posterior distributions of response rates of plasma HIV-1 RNA <50 c/mL for the optimal dose and the reference treatment.

9.2. Sample Size Determination

Approximately 160 participants will be screened to achieve approximately 80 randomly assigned to study intervention for an estimated total of 20 evaluable participants per GSK3640254 + DTG and DTG + 3TC arm. However, as a result of the potential impact of the parallel Phase 2b trial, Study 208379, the enrolment of Study 212483 may be adaptive resulting in no more than 30 participants originally randomized to any treatment arm.

The planned sample size of approximately 20 participants per active arm and approximately 20 participants assigned to the reference arm is based on the primary efficacy endpoint of FDA Snapshot response rate at Week 24 (proportion of participants with plasma HIV-1 RNA <50 c/mL). Since the analysis will be conducted using Bayesian methodology, the sample size was determined using robust simulation rather than a closed form equation.

Considering the small sample size of the study, response rate 90% (N=18) is used for the reference arm, and a response rate of 78% on the optimal dose, the probability of declaring positive sign of efficacy is approximately 27.5%. Given the stage of this phase 2b study and the relatively small sample size of each arm, this is considered acceptable. Conversely, assuming a response rate of 90% on the optimal dose, the probability of declaring a positive sign of efficacy would be 78.4%.

Selected probabilities of declaring a positive efficacy sign (defined as the optimal dose having a posterior probability of being within a 12% non-inferiority margin compared to

the reference treatment of at least 75%) are presented as the first row in Table 12 in Section 9.2.1.

9.2.1. Sample Size Sensitivity

As described in Section 4, a recommendation from the Study 208379 IDMC Week 12 analysis could result in one or two arms in this trial (212483) to be discontinued. If either or both of these arms were in fact 150 and/or 200 mg, these participants may be re-randomized to existing experimental arms. The decision will also stop the enrollment on these dropped arms. Subsequently, the remaining study arms may enroll 20-30 patients in each arm. The Bayesian analysis described in Section 9.1 will solely evaluate participants who originally received the blinded GSK3640254 optimal dose or blinded 3TC from Day 1 of the study. Any participant who changed arms (or doses) will not be included in the Bayesian analysis.

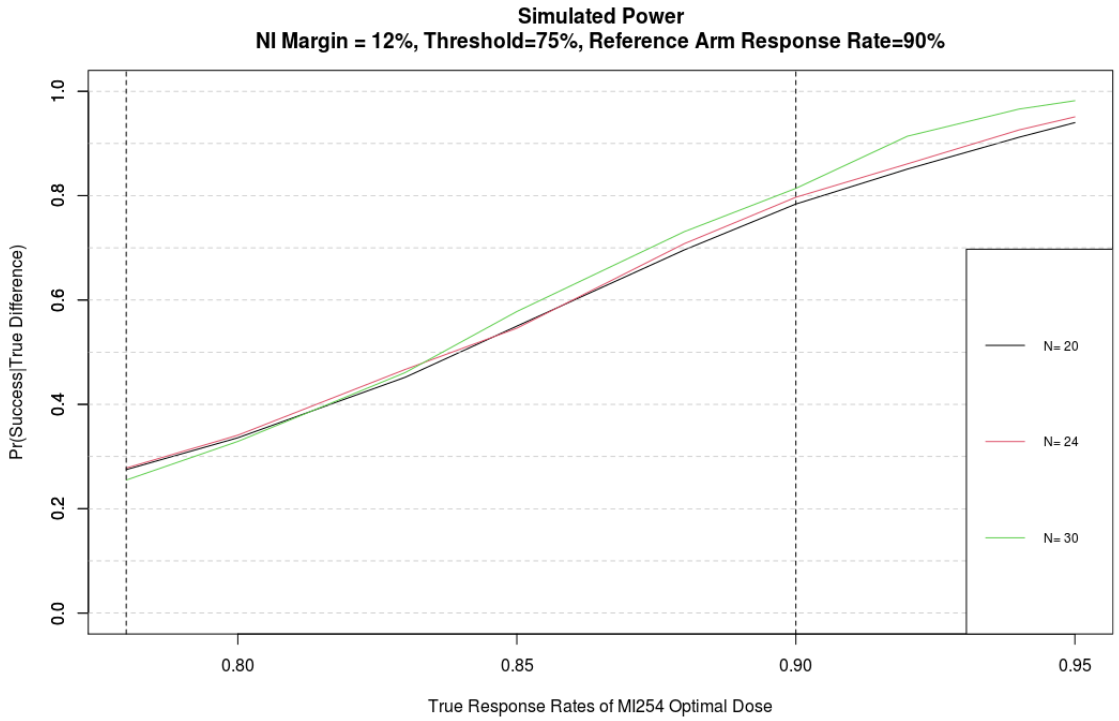
Simulations were conducted using various numbers of participants on the optimal GSK3640254 dose and the same number of participants for the reference arm in the range of [30,40]. In simulation, noninformative prior Beta(1,1) is utilized in the Bayesian model for both the optimal dose and reference arms to ensure the balanced design and apply the fair comparison between two arms.

Under the same decision rule, the number of participants greater than 20 (N>20) resulted in modest increases in the probability of correctly declaring a positive efficacy sign at high response rates (> 80%) and minimal change in the probability of incorrectly declaring positive efficacy at relatively low response rates (≤80%). Table 12 along with Figure 3 shows the response rates with the various sample sizes explored.

Table 12 Simulated power under various realistic response rates of optimal GSK3640254 dose with different sample size N

N Per Arm	Response Rate of optimal dose of GSK3640254								
	78%	80%	83%	85%	88%	90%	92%	94%	95%
20	0.275	0.336	0.452	0.55	0.696	0.784	0.851	0.912	0.94
24	0.278	0.341	0.467	0.546	0.708	0.797	0.861	0.926	0.951
30	0.255	0.329	0.461	0.578	0.731	0.814	0.914	0.966	0.982

Figure 3 Probability of a Positive Efficacy Sign at Various Sample Sizes Scenarios



Note: N is number of participants on optimal dose given various randomization situations, and the same number for reference arm.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who are randomized to receive study intervention
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.3.1. Intent-to-Treat Exposed Population (ITT-E)

The ITT-E population consists of all randomized participants who received at least one dose of study intervention. Participants will be analyzed according to the randomized treatment regardless of what treatment was actually received. Unless stated otherwise, the ITT-E population will be the primary population for efficacy analyses.

9.3.2. Per Protocol Population (PP)

This population will consist of participants in the ITT-E population with the exception of participants with significant protocol violations as defined in the SAP of this study. The PP population will be a secondary population for efficacy purposes.

9.3.3. Pharmacokinetic Population

The pharmacokinetic (PK) population will include all participants who receive GSK3640254, undergo sparse PK sampling during the study, and provide evaluable GSK3640254 plasma concentration data, demographic and baseline characteristics, and/or information on concomitant medications. Participants in this population will be included in the Population PK analysis. A population PK analysis will be done under a separate Population-PK Reporting and Analysis Plan.

9.3.4. Safety Population

The Safety Population consists of all randomized participants who were exposed to study intervention with the exception of any participants with documented evidence of not having consumed any amount of study intervention. Participants will be analyzed according to the actual treatments received. The safety population will be the primary population for safety analyses.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Release (DBR) and will include a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy statistical analysis will be based on the proportion of participants in the ITT-E population with plasma HIV-1 RNA <50 c/mL at Week 24 using the FDA Snapshot algorithm. The posterior probability of response rate of the optimal GSK3640254 dose within 12% margin of the reference arm will be produced. Besides, Bayesian posterior mean of response rate and associated 95% credible interval, frequentist point estimate and 95% confidence intervals will be derived and displayed. Full details of the planned Bayesian analyses will be provided in the SAP.
Secondary	Secondary statistical analyses will be based on the proportion of participants in the ITT-E population with plasma HIV-1 RNA <50 c/mL at Weeks 48 using the FDA Snapshot algorithm. Full details will be provided in the SAP.
Exploratory	Will be described in the SAP

9.4.2. Safety Analysis

The study is designed to select a dose for further evaluation on the basis of tolerability and virological efficacy in conjunction with immunological response, safety and pharmacokinetic measures. Measures of safety and tolerability will be used to compare the doses in a pre-specified manner will be detailed in the statistical analysis plan of the study. Exposure to study medication, measured by the number of weeks on study intervention, will be summarized by treatment arm. The proportion of participants reporting adverse events (AEs) will be tabulated for each treatment arm. The following summaries of AEs will be provided:

- Incidence and severity of All AEs;
- Incidence and severity of treatment related AEs;
- Incidence and severity of AEs leading to withdrawal from study;
- Incidence of SAEs

Laboratory data, vital signs and ECG data (absolute values and change from baseline) will be summarized by visit and treatment group. More detailed safety analyses will be described in the statistical analysis plan and will be performed on the Safety Population.

9.4.3. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

If data permits, the pharmacokinetics of GSK3640254 in combination with DTG will be determined using a non-linear mixed effects modeling approach. Population pharmacokinetic parameters will be estimated. Dependent on the final structural pharmacokinetic model, additional pharmacokinetic parameters may also be estimated. Sources of variability in pharmacokinetic parameters will be investigated during population modeling. Demographic parameters including, but not limited to age, sex, race, body weight, body mass index, concomitant medications, relevant laboratory parameters, and any additional parameters, will be evaluated as potential predictors of inter- and intra-participant variability for pharmacokinetic parameters. Population pharmacokinetic modeling will be performed using the non-linear mixed effects software NONMEM. The individual post-hoc PK parameters will be estimated and documented for the purposes of any subsequent exposure response (Pharmacokinetic/Pharmacodynamic) analyses. Further details of population pharmacokinetic analyses will be described in the Modeling Analysis Plan (MAP).

9.4.3.1. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory analyses will be performed to examine the relationship(s) between plasma concentrations of GSK3640254 in combination with DTG and pharmacodynamic endpoints. A population pharmacokinetic/pharmacodynamic modeling approach may be further applied to model the data using the nonlinear mixed effect modeling software, NONMEM. Further details of population pharmacokinetic/pharmacodynamic analyses will be described in the MAP.

9.5. Other Analysis

The overall proportion of study intervention taken relative to the planned amount will be estimated via pill counts and summarized by treatment arm for each IP.

Data from C-SSRS assessments will be summarised by visit.

Pharmacokinetic, analyses will be described in the SAP. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

Additionally, special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the main study SAP; alternatively, a separate SAP focusing on modified data handling rules (e.g., changes to analysis populations, visit windows and endpoints) and analyses (e.g., sensitivity analyses to assess impact of and account for missing data) may be prepared, taking in to account applicable regulatory guidance and industry best practices for handling such situations [FDA, 2020; EMA, 2020a; EMA, 2020b].

9.6. Interim Analysis

At least two interim analyses will be performed throughout the course of the study:

- The primary analysis will be conducted to evaluate the efficacy, safety and tolerability of optimal dose of GSK3640254 + DTG when all participants have completed their Week 24 visit

- At least one IDMC interim analysis at one timepoint prior to the Week 24 primary endpoint will be necessary as described in Section 9.6.1.

Finally, a secondary and End of Study analysis will be conducted to characterise the long-term safety, tolerability and durability of antiviral response of the optimal dose of GSK3640254 + DTG when all participants have completed their Week 48 visit.

Further data cuts and analyses may be conducted as necessary to support regulatory submissions and/or publications. No adjustment for multiplicity caused by repeated analysis on the primary endpoint will be made as the interim analysis will be secondary. Type I error rate will not be inflated for the treatment comparison at the final analysis as non-inferiority will not be assessed at the interim.

The ITT-E population will be the primary efficacy population and the safety population will be the primary safety population for any interim analysis. The actual dosage for participants randomized to a GSK3640254 arm and whether they are blinded to GSK3640254 or 3TC in combination with unblinded DTG will remain blinded to the study team until Week 24 database lock.

9.6.1. Independent Data Monitoring Committee

This study will utilize an Independent Data Monitoring Committee (IDMC) to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of participants and to protect the scientific validity of the study. An ad-hoc review of data by the IDMC will be triggered when the number of participants exceeds thresholds pre-specified in the IDMC charter for either: protocol-defined virologic failure criteria or number of safety/tolerability events. In addition, the IDMC will be triggered at least at one timepoint prior to the Week 24 primary endpoint (independent of an event based trigger). Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

  Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

  Applicable ICH Good Clinical Practice (GCP) Guidelines

  Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- 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/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable),), 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/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 (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- Participants who are rescreened are required to sign a new ICF(s).

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

The ICF contains 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/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Safety Data Review by Safety Review Teamand IDMC

- Participant safety will be continuously monitored by the Sponsor's internal safety review committee, which includes safety signal detection at any time during the study
- In addition, an independent safety review by an IDMC for this study will occur prior to the Week 24 primary endpoint (see Section 9.6.1)
- Case unblinding may be performed for above reviews, if necessary.

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 ViiV Healthcare/GSK site or other mutually-agreeable location.
- ViiV Healthcare/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 patients 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, ViiV Healthcare/GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- ViiV Healthcare/GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with ViiV Healthcare/GSK Policy.
- ViiV Healthcare/GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy 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 or equivalent CRO document.
- 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 (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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 Source Data Acknowledgment or CRO equivalent document.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. 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 participant Screening that is registered into the IVRS/IWRS is considered the first act of recruitment and will be the study start date.

Study/Site Termination

ViiV Healthcare, 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 ViiV Healthcare. 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 13 will be performed by the central laboratory. The total blood volume in this study is approximately 720 mL.

Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

- Protocol-specific requirements for inclusion or exclusion of participant 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 13 Protocol-Required Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN Amylase, Lipase	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine eGFR or Creatinine Clearance[3]	Sodium, Bicarbonate, and Chloride	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (can be nonfasting; though fasting on days when fasting lipids are collected)	Calcium, Magnesium, and Phosphate Alkaline phosphatase[2]	Creatinine Phosphokinase (CPK)	Fasting Lipid Panel (Cholesterol, Triglycerides, High density lipoprotein [HDL], low density lipoprotein [LDL])

Laboratory Assessments	Parameters
Routine Urinalysis	• Albumin • Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy Testing	• Highly sensitive serum/urine human chorionic gonadotropin (hCG) pregnancy test (as needed for participants of childbearing potential)
Other Tests	• Follicle-stimulating hormone and estradiol • Urine Drug Screen (to include at minimum: amphetamines, barbiturates, cocaine, MDMA, phencyclidine, opiates, oxycodone, cannabinoids, benzodiazepines, methadone, methamphetamines and tricyclic antidepressants) • HIV-1 RNA • CD4+ and CD8+ T-lymphocyte counts, CD4+/CD8+ T-cell count ratio • Hepatitis B: hepatitis B virus surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (with reflex to HBV DNA) • Hepatitis C: hepatitis C virus antibody (HCVAb) with reflex to HCV RNA, if positive • Serum albumin • PT/INR • rapid plasma reagin (RPR) • Gamma glutamyl transferase [GGT] and glutamate dehydrogenase [GLDH] • International normalized ratio (INR)

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6.
2. If alkaline phosphatase is elevated, consider fractionating.
3. Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-creatinine) [Levey, 2009]. In addition, GFR will be estimated by the central laboratory using the CKD-EPI-cystatin C [Inker, 2012] at Screening/Day 1 and when indicated by renal toxicity criteria

MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, PT/INR = prothrombin time/international normalized ratio

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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 SAE

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.

An SAE is defined as any serious adverse event that, at any dose:
• 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≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as 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. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life Threatening)
- Grade 5 (Death)

Where a DAIDS toxicity scale is not available for a particular event or parameter, then the investigator will instead make an assessment of intensity using their clinical judgement based on the DAIDS scale.

- **Note:** An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/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 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 ViiV Healthcare/GSK/Syneos Health.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV Healthcare/GSK/Syneos Health 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 ViiV Healthcare/GSK/Syneos Health 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 ViiV/Healthcare/GSK/Syneos Health within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK/ViiV Healthcare/Syneos Health

SAE Reporting to ViiV Healthcare/GSK/Syneos Health via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to ViiV Healthcare/GSK/Syneos Health 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 will capture the SAE Causality in the participant's source notes in a timely manner and the investigator or an appropriately delegated team member will enter the causality into the eCRF. Clinical research associates (CRAs) will monitor the subject source documentation to confirm that SAE causality is being documented by the Investigator in a timely manner.. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to ViiV Healthcare/GSK/Syneos Health 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 the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Participants of Childbearing Potential (POCBP)

Participants who are female at birth in the following categories are considered POCBP (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 participants who are female at birth 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 is required.
    - Participants who are female at birth 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:

The list does not apply to participants of childbearing potential with same sex partners or for participants of childbearing potential who are and will continue to be abstinent from

penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Methods of contraception are categorized by their effectiveness and user dependency: 1) highly effective methods (failure rate of <1% per year when used consistently and correctly) that have a low user dependency, 2) highly effective methods that are user dependent, and 3) effective methods that are not *highly* effective (failure rate of ≥1% per year when used consistently and correctly, e.g., condoms, cervical cap, diapraghm, sponge).

GSK3640254 and DTG are not genotoxic.

There are no contraceptive requirements for participants who are male at birth based on data for GSK3640254 and the most recent data for DTG.

GSK3640254 has an "unlikely" risk for teratogenicity/fetotoxicity and would allow the use of contraceptive methods both *highly effective* and *effective*. However, DTG has a "possible" risk for teratogenicity/fetotoxicity and appropriate methods of contraception are thus limited to only those methods that are considered to be *highly effective*. Because there is a DTG component in all 4 treatments arms over the course of the study, POCBP will need to adhere to the following highly effective methods of contraception:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE: If a hormonal method is selected, the POCBP is required to be clinically stable on it for at least one month prior to starting treatment in the study.
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential 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.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation • oral • injectable
• Sexual abstinence

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
If a hormonal method is selected, the POCBP is required to be clinically stable on it for at least one month prior to starting treatment in the study.
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 participants 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 (LAM) 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: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to study intervention or HIV and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to study intervention or study interventions of this drug class, and HIV. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention (or study interventions of this class) or HIV continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If Baseline ALT ≤ 1.5x ULN	
ALT-absolute	ALT ≥ 5X ULN
ALT Increase	NONE for this study.
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
Symptomatic[3]	ALT ≥ 3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If Baseline ALT > 1.5x ULN	
ALT-absolute	ALT ≥ 5x ULN OR > 500 U/L (whichever occurs first)
ALT Increase	ALT ≥ 3x baseline but < 5x ULN persists for ≥ 2 weeks (with bilirubin <2x ULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3x baseline OR > 300 U/L (whichever occurs first) **and** bilirubin ≥ 2x ULN
Cannot Monitor	ALT ≥ 3x baseline but < 5x ULN and cannot be monitored every 1-2 weeks
Symptomatic[3]	ALT ≥ 3x baseline and symptoms (new or worsening) believed to be related to liver injury or hypersensitivity)

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**

• Immediately discontinue study treatment.
• Report the event to the medical monitor **within 24 hours**.
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]**.**
• Perform liver event follow up assessments.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).
 	
MONITORING:
• Make every reasonable attempt to have participants return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments at the central laboratory as described to the right.
• A specialist or hepatology consultation is recommended.
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline.
	• Viral hepatitis serology, including:
	  • Hepatitis A immunoglobulin M (IgM) antibody;
	  • HBsAg and hepatitis B core antibody;
	  • Hepatitis C RNA;
	  • Hepatitis E IgM antibody.
	• Cytomegalovirus IgM antibody.
	• Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
	• Syphilis screening.
	• Drugs of abuse screen, including alcohol. Record alcohol use on the liver event CRF
	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must contact the medical monitor when this test is required.
	• Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4].
	• Serum CPK and lactate dehydrogenase (LDH).
	• Gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin
	• International normalized ratio (INR)
	• Fractionate bilirubin, if total bilirubin ≥1.5xULN.

	• Obtain complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant 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.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. PK sample may not be required for participants known to be receiving non-ViiV comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3x baseline and <5x baseline and bilirubin <2x ULN without symptoms believed to be related to liver injury or hypersensitivity	• Notify the medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return every 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5×ULN on 2 consecutive evaluations) • If at any time participant meets the liver chemistry stopping criteria, proceed as described above.

Asymptomatic Liver Enzyme Elevations

For asymptomatic participants who have ALT≥3X ULN, following discussions with medical monitor, ALT and other specific lab tests can be repeated in an unscheduled visit. This may include liver panel tests included in study protocol, even though participant did not meet any liver monitoring or liver stopping criteria above.

10.7. Appendix 7: Child-Pugh Classification

A participant is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following Table (Table 14). For participants requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 14 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade[1]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

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

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

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, all deaths related to an AE are to be classified as **Grade 5.**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading Table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

U.S. Department of Health and Human Services, 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] is available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

10.9. Appendix 9: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (see Section 10.8). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 10.3.5.

Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study treatment at the discretion of the investigator. Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by study treatment, dosing may continue after discussion with the medical monitor.

Participants who develop a Grade 3 AE that the investigator considers related or possibly related to the study interventions should have study treatment discontinued.

Should the same Grade 3 AE recur within 28 days in the same participant, study treatment should be permanently discontinued, and the participant withdrawn from study. Participants experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and have withdrawal study evaluations completed. A Follow-up visit should be performed 4 weeks after the last dose of study intervention.

Participants with asymptomatic Grade 3 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue study intervention if the investigator has compelling evidence that the toxicity is not related to study treatment.

Exceptions are noted for lipid abnormalities (for example, isolated Grade 3 lipid abnormalities do not require withdrawal of IP) and rash in Section 10.9.7.

Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have study treatment discontinued. However, for Grade 4 toxicities only (not AEs), if the investigator has compelling evidence that the toxicity is not causally related to the study interventions, dosing may continue after discussion with and assent from the medical monitor. Participants should be rechecked each week until the toxicity returns to Grade 2.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above.

CCI

[redacted]

Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to study treatment are provided below.

Participants who permanently discontinue study treatment for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations (see Section 1.3).

10.9.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology during administration of study intervention and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 7.1.2 and Section 10.6.

10.9.2. Hypersensitivity Reaction

Hypersensitivity reactions have been reported with integrase inhibitors, including DTG, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue DTG and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with DTG or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Participants may continue study intervention for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study intervention should permanently discontinue study treatment and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE.

10.9.3. Rash & Skin Reactions

10.9.3.1. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RM2007/00683/14].

Skin and Subcutaneous disorders have also been reported across clinical trials with GSK3640254.

Grade 1 Rash: Participants with an isolated Grade 1 rash may continue study intervention at the Investigator's discretion. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Grade 2 Rash: Participants may continue study intervention for an isolated Grade 2 rash. However, study intervention (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with any systemic signs, allergic symptoms, or if mucosal involvement develops.

Grade 3 Rash: Participants should permanently discontinue study intervention (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 rash, except where the aetiology has been definitively diagnosed as NOT attributable to study intervention (see below). Participants should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g., viral infection) or start of concomitant medication.

Grade 4 Rash: Participants should permanently discontinue study intervention (and all other concurrent medication(s) suspected in the Investigators causality assessment). Participants should be treated as clinically appropriate and followed until resolution of

the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g., viral infection) or start of concomitant medication.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings, Section 10.8).

10.9.4. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Schedule of Activities (Section 1.3). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study intervention.

10.9.5. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins), physical activity or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study interventions, study treatment should be discontinued, and the participant withdrawn from the study.

10.9.6. Decline in Renal Function

Participants who experience an increase in serum creatinine from Baseline of 45 micromoles/liter (µMol/L) (or 0.5 milligrams/deciliter [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI cystatin C method [Inker, 2012] should also be done at this confirmatory visit (refer to the SRM for details on the collection and processing of these urine samples). If the creatinine increase is confirmed, the investigator should contact the Medical Monitor to discuss additional follow-up and medical management.

Participants who experience progression to an estimated GFR (using the CKD-EPI method) [Levey, 2009] of <50 mL/min must return for a confirmatory assessment within 2 weeks. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI cystatin C method [Inker, 2012] should be done at this confirmatory visit (refer to the SRM for details on the collection and processing of these urine samples).

If an estimated GFR of <50 mL/min is confirmed, then study medications should be discontinued and the participant withdrawn.

10.9.7. Proximal Renal Tube Dysfunction

PRTD is defined as:

- Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL;
- Either of the above accompanied by any two of the following:
    - Glycosuria (≥250 mg/dL) in a non-diabetic;
    - Low serum potassium (<3 mEq/L);
    - Low serum bicarbonate (<19 mEq/L).

Participants meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed, participants must be withdrawn from the study.

10.9.8. Proteinuria

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine albumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study medical monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 μmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study medical monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and medical monitor.

Refer to the SRM for details on the collection and processing of urine samples.

10.10. Appendix 10: CDC Classification for HIV-1 Infection (2014)

- Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.

- **HIV infection, stage 0**

- Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

- **HIV infection, stage 1**
  - Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

- **HIV infection, stage 2**

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
  - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
  - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

- **HIV infection, stage 3 (AIDS)**

- Laboratory confirmation of HIV infection, and
  - CD4+ T-lymphocyte count of <200 cells/μL, or
  - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
  - Documentation of an AIDS-defining condition (see below).

- Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

- **HIV infection, stage unknown**
  - Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.

- **Stage-3-defining opportunistic illnesses in HIV infection**

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary

- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

10.11. Appendix 11: COVID-19 Pandemic and Clinical Trial Continuity

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

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to ensure that there are no gaps in HIV-1 treatment for participants enrolled in this clinical study, through continuous access to antiretroviral therapy.

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

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

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

10.11.1. Changes to Study Visits and Study Procedures

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants:

- When site staff resources are limited due to COVID-19, abbreviated study visits may proceed without conducting all protocol-specified additional assessments (e.g. lab tests, questionnaires, etc.). If laboratory testing will be missed for more than one consecutive visit, medical monitor pre-notification is required, and all efforts should be made to find alternative approaches for lab testing.
- Consider alternative travel options for participants, if possible.
- When central laboratory testing is not possible at a particular visit, tests for management of participant safety, including HIV-1 RNA may be performed at an appropriately authorised/accredited local laboratory (or other relevant clinical facility), if this can be done within local restrictions on physical distancing. The

site should proactively inform the Sponsor about such instances. Local laboratory results done as per routine follow-up, including HIV-1 RNA, may be used to inform safety and participant management decisions. Results should be retained in source records and added to the eCRF.

  - If labs are collected on site and cannot be processed (either via central lab shipping, or local labs), freeze (and maintain at correct temperature for later processing) those samples that are sent frozen. Please safely discard ambient samples per site standards.

- When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including AEs/SAEs, from the participant through alternative means, e.g. by telephone contact or video app such a Skype, FaceTime, Zoom, etc., where allowed.
  - The assessment should include inquiries to determine if the participant has been impacted by COVID-19 (extent of travel restriction, have they been in contact with any known positive cases [See Section 10.11.5.2 for WHO definition of "contact" - it is important to understand who among our participants could be at risk], assess for COVID-19 as part of the AE/SAE assessment, and inquire about any possibility that the participant has plans to be on an experimental agent for COVID-19 See Section 10.11.4)
  - Other protocol assessments and procedures as specified in the Schedule of Activities should be completed where possible (e.g. answer questions, update concomitant medications, emphasize adherence, plan/schedule participants return for next scheduled visit). This information should be placed in source records and entered into the eCRF when next possible.
  - The eC-SSRS assessment is already planned to be done via telephone in this study, whether the participant is on site for an in-clinic visit or at home and doing a virtual visit. When the participant is unable to be in the clinic for a required on-site visit, the eC-SSRS is still able to be performed at home, preferably prior to virtual contact by the site. Plans for addressing any positive results and referring for care remain no matter from which location the eC-SSRS is phoned in.
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.
- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and performance of ECGs. It is the responsibility of the investigator to inform GSK/ViiV Healthcare/Syneos Health when this occurs and to document in source notes.
- It may become necessary for the Sponsor to broadly incorporate the use of home healthcare staff to perform visits in the participant's home. This possibility is also discussed in the ICF.
- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties

temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.

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

10.11.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

Any updated informed consent form or other participant-facing materials should be provided to participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

The changes to the protocol, including COVID-19 related changes may be implemented before an ICF including COVID-19 related updates will be signed.

10.11.3. Direct-To-Patient (DTP) Shipment of Study IP

If a participant is unable to attend a study visit or to come to the site to pick-up investigational product (IP) due to site restrictions, or due to an inability to travel to the site (for personal precaution/sequestration, or government mandated travel restrictions, etc.), sites can consider DTP shipments of drug, from the site, to the participant, to ensure access to medicines. All other options, including alternative travel options for participants, should be considered before reverting to DTP shipments.

- If the study site is considering DTP shipment of IP, the site must first verify if DTP IP dispensing by investigators/hospital pharmacies is locally permitted and **whether it requires regulatory and/or local ethics pre-approval, or post-hoc notification.**
- The study participant will express his/her agreement for DTP shipment and the sharing of their personal information with any third-party couriers (as applicable), in accordance with local requirements. This agreement will be documented within the main ICF.

- DTP IP should be supplied only in a quantity that is sufficient to cover the interval to the next scheduled dispensation visit. There is a risk that accompanies dispensing more than a single 3-bottles set of blinded GSK3640254. Please see the SRM for details about the limitations with dispensation.
- GSK/ViiV Healthcare suggest the use of Marken in most countries for DTP shipments. Otherwise, ensure local courier vendors, or vendors of hospital pharmacies, can ensure proper in-transit temperature monitoring, have enough shipper boxes and temperature loggers and can document storage conditions during IP transportation.
- Where temperature monitoring is not available, oral protocol study treatments can be shipped at ambient temperatures with couriers that can provide shipper boxes capable of maintaining the shipment temperature storage requirements as described in the study guides. The risk of going outside of the excursion ranges listed in the study guide should be evaluated and documented. Proper documentation of the shipment should be maintained. In all cases IP accountability must be maintained, and all DTP dispensing documentation should be reflected in source records and dispensing logs per GCP.
- Please refer to your CRA or local study manager for support with the DTP process, ensuring reference to current sponsor guidance and arrangement of a courier that can support shipment of IP directly to participants.
- Remember that any courier deliveries can be affected by limitations of movements imposed by governments in relation to COVID-19.
- Local courier vendors should be equipped to reduce risks of COVID-19 contamination during transportation.

10.11.4. COVID-19 Therapeutic Agents

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

The protocol does not allow for concurrent enrolment in other interventional studies.

10.11.5. COVID-19 Specific Data Capture

10.11.5.1. Capturing COVID-19 Specific Protocol Deviations

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

10.11.5.2. Capturing COVID-19 Specific AEs and SAEs

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

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.
2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.
3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve; the most recent definitions should be consulted for each case (WHO). When reporting both serious and non- serious adverse events (related to COVID-19 infection), investigators should use the following Verbatim terms:

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

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study intervention continuation in the setting of clinically defined mild COVID-19 infection.
5. A new COVID-19 infection Case Report Form is included in the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important that the correct information is collected from each participant reporting a COVID-19 AE or SAE. Therefore, please use the CRF templates to help you collect this information for all COVID-19 related AEs/SAEs.

10.11.5.2.1. WHO Case Definition (July 15, 2022 Version or later):

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-2022.1 or the current applicable version at the time of a potential COVID case.

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.

10.12. Appendix 12: Abbreviations and Trademarks

3TC	Lamivudine
ABC	Abacavir
ADME	absorption-distribution-metabolism-elimination
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
AST	Aspartate aminotransferase
ART	Anti-retroviral therapy
ARV	Anti-retroviral
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
AUC(0-24)	Area under the plasma concentration time curve from zero to 24
AVB	Atrioventricular block
β-HCG	Human chorionic gonadotropin
BDC	Bile-Duct-Cannulated
BMI	Body mass index
BMS	Bristol-Myers Squibb
bpm	Beats per minute
cART	Combination anti-retroviral therapy
c/mL	Copies per millilitre
C0	Concentration, pre-dose
C24	Concentration, 24 hours post-dose
CAp24	Capsid protein 24
CD4	Cluster of designation 4
CD8	Cluster of designation 8
CDC	Center for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO	Chief Medical Officer
CMV	Cytomegalovirus
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRA	Clinical research associate
CrCl	Creatinine Clearance
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale

Ct	Concentration at end of dosing interval
CV	Cardiovascular
CVb	Between-participant coefficient of variation
DAIDS	Division of AIDS
DBR	Database Release
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
DTG/ABC/3TC	Triumeq
EC50	Effective concentration
EC90	Effective concentration
EGD	Esophagogastroduodenoscopy
ECG	Electrocardiogram
Emax	Effect, at the maximum
EMEA	European Medicines Agency
FACTS	Fixed and Adaptive Clinical Trial Simulation
FAST	Focused Assessment with Sonography in Trauma
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FSH	Follicle Stimulating Hormone
FTIH	First-time-in-human
Gag	Group-specific antigen
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
h or hr	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C antibody
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human immunodeficiency virus-1
HRT	Hormonal replacement therapy
HSR	Hypersensitivity Reaction
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INI	Integrase Inhibitor
INR	International normalized ration
IQ	Inhibitory quotient
IRB	Institutional Review Board

INSTI	Integrase Strand Transfer Inhibitor
IP/IMP	Investigational Product/Investigational Medicinal Product
IRT	Interactive Response Technology
iSRC	Internal Safety Review Committee
ITT	Intent to treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
kDa	Kilodalton
kg	Kilogram
lbs	Pounds
LDL	Low density lipoprotein
LOAEL	Lowest observed adverse effect level
LLOD	Lower limit of detection
LOC	Local Operating Company
MAD	Multiple ascending dose
MAP	Modeling Analysis Plan
MedRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Maturation inhibitors
MOA	Mechanisms of action
MSDS	Material Safety Data Sheet
ms, msec	Milliseconds
NOAEL	No-observed-adverse-effect-level
NIMP	Non-investigational Medicinal Product
nM	nanomolar
NPO	nil per os (Nothing by mouth)
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non- Nucleoside Reverse Transcriptase Inhibitor
OCT2	Organic Cation Transporter 2
PBAEC90	Protein binding adjusted concentration
PBO	Placebo
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDVF	Protocol-Defined Virologic Failure
PI	Principal Investigator
PK	Pharmacokinetic
POC	Proof of Concept
PRSAE	Possible Suicidality-Related AE
PGX	Pharmacogenetics
POCBP	Participant of Childbearing Potential
PP	Per protocol
PPI	Proton pump inhibitor
PPL	Physician Product Lead
PRTD	Proximal Renal Tubule Dysfunction

PSRAE	Possible Suicidality-Related AE
PT/INR	Prothrombin time/International normalized ratio
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
QTL	Quality Tolerance Limit
R	Accumulation ratio
RBC	Red blood cells
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin
SAD	Single ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SI	Sub-Investigator
SOA	Schedule of activities
SOC	System Organ Class
SP1	Spacer peptide 1
SRDP	Study Results Dissemination Plan
SRM	Study Reference Manual
SRT	Safety Review Team
STR	Single tablet regimen
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
tlag	Absorption lag time
tmax	Time of occurrence of Cmax
TN	Treatment naïve
ULN	Upper limit of normal
VH	ViiV Healthcare
VLD	Viral load drop
VSLC	ViiV Safety and Labelling Committee
VT	Ventricular Tachycardia
WBC	White blood cells
Wk	Week

Trademark Information

Trademarks of the ViiV Healthcare group of companies
DOVATO
EPZICOM
TIVICAY

Trademarks not owned by the ViiV Healthcare group of companies
GenoSure
Leica Aperio AT2DX
Monogram Biosciences
NONMEM
PhenoSense

10.13. Appendix 13: Protocol Amendment History

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

Amendment 02: 02-SEP-2021

Study 212483 is undergoing a substantial amendment to reduce the sample size from approximately 120 participants to approximately 80 participants. This reduction of 40 participants will occur equally among the 3 experimental arms. Thus, the number of participants will be as follows (each arm in combination with open-label DTG backbone as originally described):

Arm	Original Number Participants	Amended Number of Participants
GSK3640254 100 mg	**30**	**20**
GSK3640254 150 mg	**30**	**20**
GSK3640254 200 mg	**30**	**20**
3TC	**30**	**20**
Total	**120**	**80**

The justification of this reduction in sample size is as follows:

1. The Sponsor is conducting an additional Phase 2b study (Study 208379 that began screening in November 2020) – also in Treatment Naïve adults – investigating GSK3640254 (at the same 3 doses) in combination with open-label nucleoside reverse transcriptase inhibitors (NRTI) backbone. Since the trial began screening in November 2020, approximately ~89% of sites world-wide have been activated. The Sponsor anticipated screening would complete by 18 May 2021. However, as of 01 July 2021, approximately 59 (of 150 total) have randomized. The reasons for slower than anticipated recruitment is based upon the multi-factorial impact of the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Qualitative feedback from Investigators shows the incidence of known newly diagnosed HIV-1 infection has decreased. Moreover, physicians and newly infected patients have a strong desire to immediately start antiretroviral therapy, so they are less likely to participate in this Phase 2b study, which has a screening period of approximately 42 days. Based on this, a substantial amendment is being submitted to reduce the sample size from 30 per arm to 20 participants per arm in this study.

2. Note, of approximately 109 participants initially screened in 208379, a screening Phenosense GT result is available for 22 participants. Of the 22 participants, there is ample diversity in HIV-1 sub-type as follows: Sub-type B (13 participants), Sub-type C (2 participants), and 1 participant in each of the following Sub-types: Complex, AG, G, B/G, F1, AE, A1. Thus, a smaller sample size in this study, with

the same sample population and similar geographic recruitment area would not limit diversity in HIV-1 sub-type. Preserving the diversity of HIV-1 sub-type still allows the Sponsor to evaluate the broad spectrum of efficacy of GSK3640254 (note: Gag polymorphisms, varying by sub-type, impacted prior developmental Maturation Inhibitors).

3. The Sponsor does not have formal statistical testing in this trial (212483). Note, Section 9 has been updated to describe modifications to the Statistical Considerations. The Sponsor finds the changes Type I error rate and Power to be clinically acceptable.

4. A reduction in sample size does not limit the ability to make clinical inferences on the efficacy, safety/tolerability, and resistance of an optimal dose GSK3640254 (for subsequent clinical development) – resulting in maintenance of clinical integrity and unchanged risk benefit ratio to study participants.

Justification for the removal of the Internal Sequestered Team

In order to improve the clinical and scientific rigor and independence, the Sponsor will conduct a planned interim analysis with an IDMC instead of a Sequestered Team. The timing of the interim analyses (either by time of event trigger) will be specified in the IDMC charter.

Overall Rationale for the Amendment:

This is a global protocol amendment. An update was made to the number of study participants from total 120 to 80; revised text to include changes made in the IDMC Charter to account for the reduced number of participants, revisions to the interim analysis, and the removal of the internal sequestered team; other updates were made throughout to correct errors and for clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Schema Figure Footnotes 1 and 3 were updated to reflect the changes in the IDMC reviews for Study 208379 and this study and to reflect the removal of the Sequestered internal analysis team.	Updated to incorporate changes made in this protocol amendment
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design, 6.3 Measures to Minimize Bias 10.1.5.1 Safety Data Review by Safety Team and IDMC Protocol Summary, 4.1 Overall Design, 9.6 Interim Analysis, 9.6.1 Independent Data Monitoring Committee 9.6.2 Sequestered Sponsor Team Analysis	Mention of the internal Sequestered team was removed Updates on the IDMC interim analysis. Section 9. 6.2 was deleted since the internal Sequestered Team was removed from the IDMC charter	In order to improve the clinical and scientific rigor and independence, the Sponsor will conduct a planned interim analysis with an IDMC instead of a Sequestered Team to be consistent with the modified IDMC Charter.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design, 4.1.1 Screening Period 4.1.2.2 Week 24 through Week 52 9.2 Sample Size Determination 9.2.1 Sample Size Sensitivity 9.2.1 Sample Size Sensitivity Table 3 and Figure 2	Updated to reduce study sample size from 120 to 80 total participants; All treatment arms were reduced from 30 to 20 participants; The 50% Screen failure rate was thus revised from 240 to 160 participants. The decision rule was updated due to a change in sample size Update Table and Figure to reflect the new sample size	Reduction in sample size was done to improve enrolment goals so they can be met in a timely manner. The study is not powered, and the reduction does not limit the ability to make clinical inferences on the efficacy, safety/tolerability, and resistance of an optimal dose GSK3640254 (for subsequent clinical development).
1.3 Schedule of Activities	Added ± 15-minute window for each ECG measurement for clarity.	Added assessment windows around the time ECG data is collected in the schedule of activities for clarity.
1.3 Schedule of Activities 8.2.6 Suicidal Ideation and Behaviour Risk Monitoring	Updated to mention about window period of ± 7 days for completing eC-SSRS for each visit post-randomization. The visit to collect the baseline e-C-SSRS lifetime experience and current experience (within the past 2 months) was clarified to be at the Screening visit.	Text added for clarity.
4.1 Overall Design 9.2.1 Sample Size Sensitivity	Revisions to Study 208379 relating to the IDMC interim analysis. The interim analysis time-point was moved from Week 16 to Week 12	The total number of participants in 208379 was reduced in a protocol amendment and to account for changes in the IDMC Charter (i.e., updated timepoints for interim analysis).

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Added that all participants will receive 5 bottles (4 with tablets and 1 with capsules) to maintain the study blind through Week 24.	Text added for clarity.
4.1.2, 8.4 Table 11	Week 2 sample collection window reduced from 9-14 days to 11-14 days.	Window reduced to better assess HIV-1 viral load in all participants.
5.1 Inclusion Criteria	Inclusion criterion 4 was updated to decrease the screening CD4+ T-cell count from≥300 cells/mm^3 to ≥250 cells/mm^3.	To improve future recruitment based on recent experience in other internal studies based on the same treatment naïve participants.
5.2 Exclusion Criteria	Exclusion Criteria 28 was updated to when study treatment can start after treatment for syphilis infection.	Text was modified for clarity.
5.2 Exclusion Criteria	Exclusion 22 was updated to include: Historical evidence of the presence of resistance to the integrase inhibitor class or to lamivudine.	New text added.
5.2 Exclusion Criteria	Country specific exclusion criteria were added (Exclusion criteria 37 and 38)	France specific request
5.3.3 Activity	Removed the following text: Participants may engage in light recreational activities during studies (e.g., watching television, reading).	Text was deleted as it was not correct for this study. The prior sentence in this section was correct.
8.2.3 Cardiac Monitoring with Electrocardiograms	Removed text that ERT may provide a cardiologist over-read of ECGs	Revised for clarity
8.2.4 Clinical Laboratory Assessments	Q2 Solutions was changed to PPD central lab.	Study changed the central lab vendor.

Section # and Name	Description of Change	Brief Rationale
9.2 Sample Size Determination	The probability of declaring positive sign of efficacy was modified to approximately 27.5%. The probability of declaring a positive sign of efficacy would be 78.4%.	Changes to same size determination were modified due to the lower sample size.
9.6 Interim Analysis	Added the potential for additional data cuts and analysis.	Clarification to add that additional data cuts or analysis could be required for regulatory submissions or publications.
10.2 Clinical Laboratory Tests	Added the approximate total study blood volume (720 mL)	Text added
10.2 Clinical Laboratory Tests, Table 13	Added a new footnote 3 with reference to Glomerular filtration rate (GFR) Deleted acronym definitions that are not used in this protocol	Correction to the footnotes
10.3.5 Reporting of SAE to GSK/ViiV Healthcare/Syneos Health	Revised text to state SAE causality will be documented in the source documents in a timely manner prior to the entry into the eCRF. CRAs will monitor source documentation to confirm that SAE causality is being documented in a timely manner.	GSK Process change.
10.11.4 COVID-10 Therapeutic Agents	Updated COVID-19 agents from 'experimental' to 'therapeutic'.	COVID-19 vaccines have been approved for use.

Amendment 01: 19-MAR-2021

This amendment is considered to be Non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This is a global protocol amendment. An update was made to the study entry criteria and minor updates were made throughout to correct errors and for clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
Title Page	Study Acronym added.	To include the study acronym (DYNAMIC).
2.3.2 Benefit Assessment	Removed the word 'preliminary' from 'Data from the Phase 2a study does show a PK/PD (decline in HIV-1 RNA) relationship (described in detail in Section 4.3).'	To correct an error.
5.1 Inclusion Criteria	Inclusion criterion 4 was updated to decrease the screening CD4+ T-cell count from≥350 cells/mm^3 to ≥300 cells/mm^3.	To improve future recruitment based on recent experience in the sister study in the Phase 2b program in a similar population.
7.1.3 Columbia-Suicide Severity Rating Scale	Section added.	For clarity and consistency.
8.3.7 Disease-Related Events and/or Disease-related Outcomes (HIV-Associated Conditions)	Text updated.	For clarity and consistency.
10.6 Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Section 7.1 Discontinuation of Study Intervention	Text updated.	To clarify that study drug must be stopped immediately when ALT ≥ 5X ULN and that restart is not permitted.
10.9.2 Hypersensitivity Reaction	Text updated.	For clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
10.9.3 Rash & Skin Reactions and 2.3.1 Risk Assessment	Text updated	To clarify that study drug should be permanently discontinued for any Grade ≥2 rash that is associated with any systemic signs, allergic symptoms, or if mucosal involvement develops.

11. REFERENCES

Aboud M, Orkin C, Podzamczer D, Bogner JR, Baker D, Khuong-Josses M.-A., et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. Lancet HIV. 2019 Sep;6 (9): e576-e587.

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

Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019 Jan 12; 393(10167); 143-155.

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

DOVATO USPI. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Dovato/pdf/DOVATO-PI-PIL.PDF. 2020.

EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic.Version 1, 20 March 2020(a).

EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. EMA/158330/2020. 25 March 2020(b).

European AIDS Clinical Society (EACS) Guidelines for the clinical management and treatment of HIV Infected Adults in Europe. Version 10.1, October 2020. Available at: https://www.eacsociety.org/files/guidelines-10.1_5.pdf. Accessed October 26, 2020.

FDA Draft Guidance: Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations, Guidance for Industry. February 2019.

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, Guidance for Industry, Investigators, and Institutional Review Boards. March 2020.

GlaxoSmithKline (GSK) Document Number 2018N379610_02: GSK3640254 Clinical. Investigator's Brochure Version 03. November 2020.

GlaxoSmithKline (GSK) Document Number RM2007/00683/14: GSK1349572 Clinical.Investigator's Brochure Version 14. September 2020.

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

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. N Engl J Med 2012; 367:20-29.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Lacy B, Mearin F, Chang L, et. al. Bowel Disorders. Gastroenterology. 2016. 150:1393-1407.

Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, et.al. A new equation to estimate glomerular filtration rate. Ann Int Med. 2009; 150: 604-12.

Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP et al. Efficacy, safety and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. 2018 March 3; 391 (10123):839-849.

Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997;3:628-37.

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.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed August 30, 2021.

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.

Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-49.

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

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

Solomon A, Tennakoon S, Leeansyah E, et al. (2014) No Difference in the Rate of Change in Telomere Length or Telomerase Activity in HIV-Infected Patients after Three Years of Darunavir/Ritonavir with and without Nucleoside Analogues in the MONET Trial. PLoS ONE 9(11): e109718. doi:10.1371/journal.pone.0109718. Available at:

http://journals.plos.org/plosone/article/asset?id=10.1371/journal.pone.0109718.PDF. Accessed February 8, 2017.

Stanghellini V, Chan FKL, Hasler W, et. al. Gastroduodenal Disorders. Gastroenterology. 2016. 150:1380-1392

TIVICAY USPI. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF#page=1. 2020.

U.S. Department of Health and Human Services, 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

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. 2015. Washington, D.C.

Van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, et al. Switching to DTG/3TC fixed-dose combination (FDC) is non-inferior to continuing a TAF based Regimen (TBR) in Maintaining Virologic Suppression Through 96 Weeks. 2020. International Congress on Drug Therapy in HIV Infection. Glasgow, Scotland.

World Health Organization (WHO). *STEPS Surveillance Manual. The WHO STEPwise approach to noncommunicable disease risk factor surveillance*, 2017; 3-5-9 to 3-5-13.

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

Signature Page for 212483 TMF-14435461 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 11-Aug-2022 14:35:00 GMT+0000

Signature Page for TMF-14435461 v1.0