Clinical Study Protocol

Primary Study Intervention(s)	VH3739937
Other Study Intervention(s)	N/A
Study Identifier	212580/Amendment 1
EudraCT Number	2021-003207-18
EU CT Number	2023-505780-37-00
Approval Date	06 Oct 2023
Title	A Randomized, Double-Blind (Sponsor-Unblinded), Placebo-Controlled, Adaptive Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH3739937 in Treatment-Naïve Adults Living with HIV-1 (PROCLAIM)
Compound Number/Name	VH3739937
Brief Title	VH3739937 Proof-Of-Concept in Treatment-Naïve Adults Living with HIV-1
Sponsor	**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 410 Blackwell Street Durham, NC 27701, USA Telephone: + 1 877 844 8872 **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. GSK is supporting ViiV Healthcare in the conduct of this study.
Sponsor signatory	Scott McCallister, MD Vice President & Head, R&D Physician Center of Excellence

Medical monitor name and contact can be found in local study contact information document

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by ViiV Healthcare/GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the ViiV Healthcare/GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of ViiV Healthcare/GSK and the express **physical and/or digital informed** consent of the participant and/or the participant's LAR.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of ViiV Healthcare/GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. ViiV Healthcare/GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply ViiV Healthcare/GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that ViiV Healthcare/GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide ViiV Healthcare/GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

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Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	06 Oct 2023
Original Protocol	01 June 2023

Amendment 1 (06 Oct 2023)

This amendment is considered non-substantial **based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union** because it neither significantly impacts the safety of participants nor the scientific value of the study**.**

Overall rationale for the current Amendment:

A request for clarification of inconsistencies in the participant discontinuation criteria described in Section 7.1 and Section 10.7 of the protocol was received from the FDA on 18 September 2023. In addition, the format of the C-SSRS that will be used in the study has been corrected from participant-completed to clinician-administered (e.g. physician, physician assistant, or advanced practice nurse). This reflects a change in company policy to use the clinician-administered version for all studies.

Additional minor clarifications, corrections and administrative changes have been made throughout.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Title page, Investigator signature page and 1.1 Synopsis	Added study acronym PROCLAIM	To add the study acronym (PROCLAIM)

Section # and title	Description of change	Brief rationale
7.1 Discontinuation of study intervention	Removed reference to renal toxicity management criteria in Appendix 7 • Updated AE discontinuation criteria to align with language used in Section 7.1.3 and Section 10.7.	There are no specific renal toxicity management criteria detailed in Appendix 7, this text was included in error. Renal toxicity should be managed as any general toxicity/AE would be managed. Changes made at FDA request to clarify inconsistencies in AE discontinuation criteria. This section has been aligned to wording in Section 7.1.3 and Section 10.7, specifically that any Grade 4 AE would result in discontinuation, regardless of relatedness to study intervention.
7.1.3 Individual Participant Laboratory Abnormality and Adverse Event Stopping criteria	Updated rash criteria to state any related Grade 3 or any Grade 4 rash would result in discontinuation.	Changes made to clarify an inconsistency between Section 7.1.3 and rash toxicity management criteria described in Section 10.7, as per FDA request.
8.3.6 Suicidal ideation and behavior risk monitoring	Revised C-SSRS description to the clinician-administered electronic C-SSRS, instead of the patient-completed eC-SSRS. References to the eC-SSRS have been updated to C-SSRS throughout the protocol.	Due to a change in company policy, all ViiV Healthcare/GSK studies will now use the clinician -administered version of the C-SSRS as standard.
8.5 Pharmacokinetics	The following updates were made to Table 7 and Table 8: • Increased the window for pre-dose procedures on Days 1-7 in Part 1A and 2A and on Day 1 in Part 1B and 2B to be -45 minutes before dosing. • Added meal window pre-dose of -25 minutes on Days 1-7 in Part 1A and 2A, and on Day 1 in Part 1B and 2B.	Section 5.3.1 requires participants eat a meal during the 25 minutes before dosing and to take their dose within 5 minutes of completing the meal. The window for pre-dose procedures has been updated to allow sufficient time for procedures to be completed before participants need to start their meal. Day 2 and Day 8 were split onto different rows as Day 8 does not include a meal and the window pre-dose procedures on that day remains -15 minutes. ECG updates were made for clarity and consistency with the SoA.

Section # and title	Description of change	Brief rationale
	• Added missing pre-dose ECGs	
8.8.1 Viral genotyping and phenotyping	Added a statement that results of genotypic and phenotypic analyses will not be shared with investigators.	The assays used to perform the genotypic and phenotypic analyses are not CE-marked for diagnostic use. As such, results of these analyses should not be used for diagnostic purposes and will not be shared with investigators.
10.1.4 Recruitment strategy	Corrected the participant numbers to be screened (50 participants) and enrolled (20 participants) in Part 2	Updated for consistency with participant numbers for Part 2 given in Section 1.2 and Section 4.1.
10.7 Appendix 7 Toxicity Management	Revised text for discontinuation related to Grade 3 Toxicity/AE and for Grade 2 Rash.	To correct inconsistencies between Section 7.1.3 and rash toxicity management criteria described in Section 10.7, as per FDA request.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
µg/mL	micrograms per milliliter
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
anti-HBs	Hepatitis B surface antibody
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC(0-168)	Area under the concentration-time curve from zero to 168h
AUC(0-24)/AUC(0-24),ss	Area under the concentration-time curve from zero to 24h/Area under the concentration-time curve from zero to 24h at steady state
AUCinfinity	Area under the plasma concentration-time curve from pre-dose to infinity
AVB	Atrioventricular block
BMI	Body mass index
c/mL	copies per milliliter
C168	Concentration at 168 h post dose
C24/C24,ss	Concentration at 24 h post dose following single dose/Concentration at 24 h post dose at steady state
CA	Competent authority
cART	Combination Antiretrovial Therapy
CDC	Centers for Disease Control
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent oral clearance
Cmax/Cmax,ss	Maximum observed concentration after single dose/Maximum observed concentration at steady state
CMV	Cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus disease
CPK	Creatinine phosphokinase
CPMS	Clinical Pharmacology Modeling and Simulation

CRA	Clinical Research Associate
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computerised tomography
Ctrough	Minimum concentration before next dose
CV	Cardiovascular
DNA	Deoxyribunucleic acid
DRE	Disease-related event
DTG	Dolutegravir
EC90	90% maximal effective concentration
ECG	Electrocardiogram
ED	Early discontinuation
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoS	End-of-study
FAS	Full analysis set
FAST	Focused Assessment with Sonography in Trauma
FDA	Food and Drug Administration, United States of America
FSH	Follicle stimulating hormone
FSFV	First subject first visit
FTiH	First-time in human
g	grams
Gag	Group-specific antigen
GCP	Good clinical practices
GERD	Gastroesophageal reflux disease
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
h or hr	hour
h*µg/mL	microgram hours per milliliter
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCVAb	Hepatitis C antibody
HDL	High density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation

ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety reports
IDSL	Integrated Data Standards Library
IEC	Independent ethics committee
IMP	Investigational medicinal product
INSTI	Integrase inhibitor
INR	International normalized ratio
IQ	Inhibitory quotient
IRB	Institutional review board
IWRS	Interactive web response system
kDa	Kilodalton
kg	Kilogram
lbs	pounds
LDL	Low denisty lipoprotein cholesterol
LLOD	Lower limit of detection
LOAEL	Lowest observed adverse effect level
MAD	Multiple Ascending Dose
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mg/mL	milligrams per milliliter
MI	Maturation inhibitor
min	Minimum
mL	milliliter
MSDS	Material Safety Data Sheet
msec	milliseconds
NIMP	Non-investigational medicinal product
nM	nanomolar
NOAEL	No observed adverse effect level
NQ	Non-quantifiable
NSAIDS	Non-steroidal anti-inlammatory drugs
PBO	Placebo
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDAP	Project data analysis plan
PI	Prediction interval
PiB	Powder in Bottle
PII	Personal identifiable information
PK	Pharmacokinetic
PLWH	People living with HIV
POC	Proof-of-Concept

POCBP	Person of childbearing potential
PONCBP	Person of nonchildbearing potential
PP	Per protocol
PR	Protease
PSRAE	Possible Suicidality-Related AE
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
QTL	Quality tolerance limit
QW	Once weekly
R	Accumulation ratio
RBA	Relative Bioavailability
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
SD	Standard deviation
SIB	Suicidal ideation behavior
SoA	Schedule of activities
SOC	Standard of Care
SOP	Standard operating procedure
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	Terminal half-life
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
tmax	Time to maximum observed concentration
TMF/eTMF	Trial Master File/electronic Trial Master File
TN	Treatment naïve
ULN	Upper limit of normal
V/F	Apparent volume of distribution
VLD	Viral load drop
VT	Ventricular tachycardia
WBC	White blood cell
WHO	World Health Organization

Term	Definition
Adverse Drug Reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Caregiver	A 'caregiver' is someone who – lives in the close surroundings of a participant and has a continuous caring role or – has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.

Term	Definition
Comparator	Any product used as a reference (including placebo, marketed product, ViiV Healthcare/GSK or non-ViiV Healthcare/GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
CRA	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study.

Term	Definition
	The terms legal representative or legally authorized representative are used in some settings.
NIMP	A NIMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Term	Definition
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., the IB for an unapproved investigational medicinal product). All ADRs that are both serious and unexpected are subject to expedited reporting
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Randomized, Double-Blind (Sponsor-Unblinded), Placebo-Controlled, Adaptive Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH3739937 in Treatment-Naïve Adults Living with HIV-1 (PROCLAIM)

Brief Title:

VH3739937 Proof-Of-Concept in Treatment-Naïve Adults Living with HIV-1 (PROCLAIM)

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

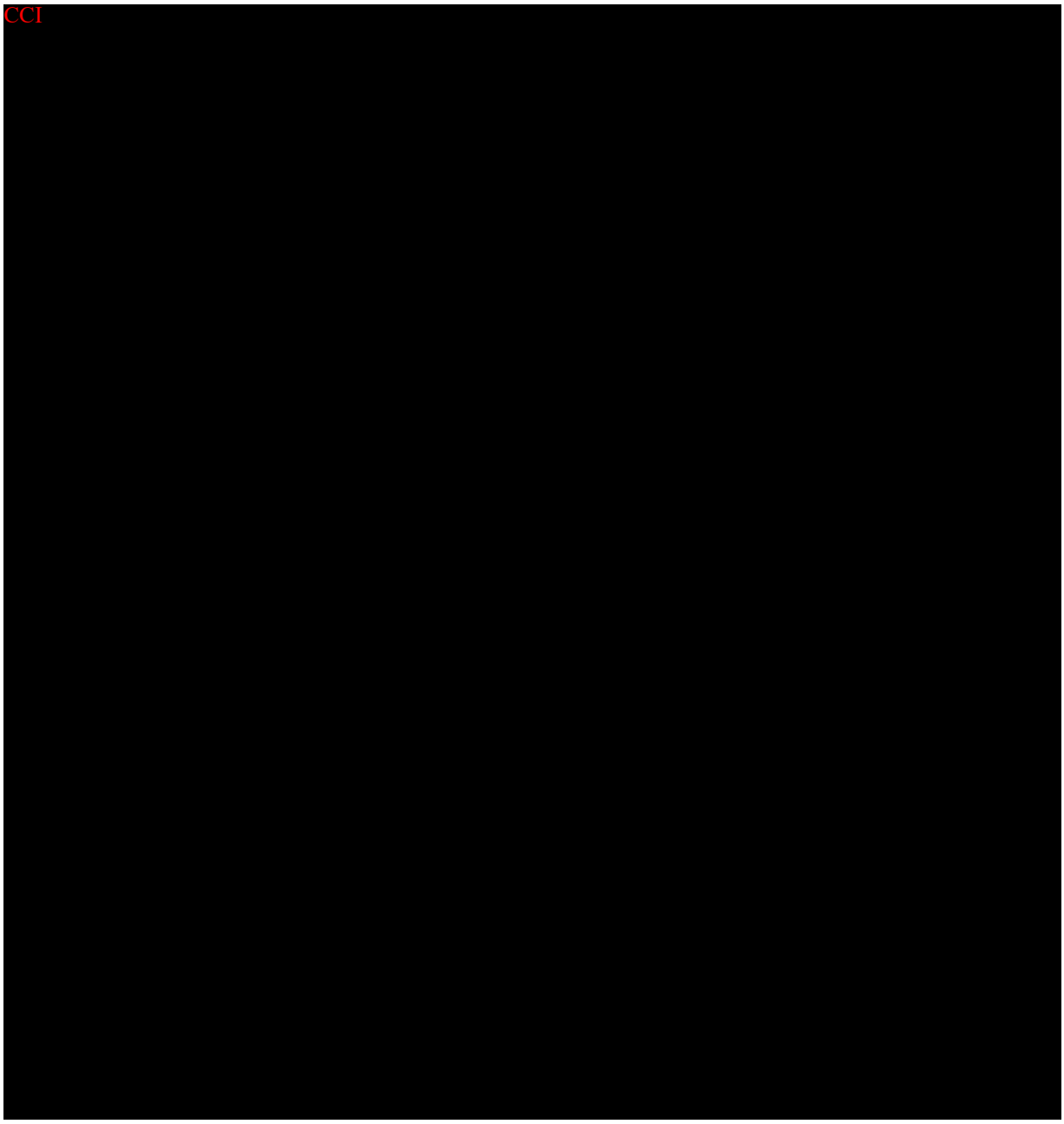
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



1.3. Schedule of Activities

Table 1 SoA

Procedure[1]	Screening[2] (7-14 days before Day 1)	Study Intervention Period Days 1-7							Post-Study Intervention Follow-up Days 8-21			Follow-up/ED[15]	Notes ED = early discontinuation/withdrawal
		Day 1	Day 2	Days 3 and 4 1 clinic visit and 1 virtual[3]		Days 5 and 6 1 clinic visit and 1 virtual[3]		Day 7	Day 8	Day 14 (+/- 1 day)	Day 21 (+/- 1 day)	Day 25 (+/- 1 day)	
		Clinic visit 1	Clinic visit 2	Clinic visit 3	Virtual[14]	Clinic visit 4	Virtual[14]	Clinic visit 5	Clinic visit 6	Clinic visit 7	Clinic visit 8	Clinic visit 9	
Outpatient Visit	X	X	X	X		X		X	X	X	X	X	
Video/phone call					X		X						
Informed consent	X												See Section 10.1.3 for details
Inclusion and exclusion criteria	X	X											Recheck clinical status before 1st dose of study medication. See Section 5.1 and Section 5.2 for Inclusion and Exclusion criteria
Demography	X												See Section 8.1.1 for more information
Medical history (includes substance usage and Family history of premature CV disease)	X												Substances: Drugs and Alcohol Premature CV disease: female participant < 65 years or male participant <

Procedure[1]	Screening[2] (7-14 days before Day 1)	Study Intervention Period Days 1-7							Post-Study Intervention Follow-up Days 8-21			Follow-up/ED[15]	Notes ED = early discontinuation/withdrawal
		Day 1	Day 2	Days 3 and 4 1 clinic visit and 1 virtual[3]		Days 5 and 6 1 clinic visit and 1 virtual[3]		Day 7	Day 8	Day 14 (+/- 1 day)	Day 21 (+/- 1 day)	Day 25 (+/- 1 day)	
		Clinic visit 1	Clinic visit 2	Clinic visit 3	Virtual[14]	Clinic visit 4	Virtual[14]	Clinic visit 5	Clinic visit 6	Clinic visit 7	Clinic visit 8	Clinic visit 9	
													55 years in first degree relatives only See Section 8.1.2 for more information
Prior ART check to ensure naïve status	X												
CDC classification	X	X											See Section 8.2 for more information
HIV-associated conditions	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2 for more information
Plasma for HIV-1 genotype/phenotype[4]		X	X	X		X		X	X	X	X	X	See Section 8.8 for more information
HIV-1 RNA	X	X	X	X		X		X	X	X	X	X	See Section 8.2 for more information
Physical examination including height and weight[5]	X	X							X			X	See Section 8.3.1 for more information
Vital signs	X	X	X	X		X		X	X	X	X	X	See Section 8.3.2 for more information
C-SSRS Administration	X								X			X	See Section 8.3.6 for more information
ECG: single reading	X												See Section 8.3.3 for more information

Procedure[1]	Screening[2] (7-14 days before Day 1)	Study Intervention Period Days 1-7							Post-Study Intervention Follow-up Days 8-21			Follow-up/ED[15]	Notes ED = early discontinuation/withdrawal
		Day 1	Day 2	Days 3 and 4 1 clinic visit and 1 virtual[3]		Days 5 and 6 1 clinic visit and 1 virtual[3]		Day 7	Day 8	Day 14 (+/- 1 day)	Day 21 (+/- 1 day)	Day 25 (+/- 1 day)	
		Clinic visit 1	Clinic visit 2	Clinic visit 3	Virtual[14]	Clinic visit 4	Virtual[14]	Clinic visit 5	Clinic visit 6	Clinic visit 7	Clinic visit 8	Clinic visit 9	
ECG: single reading pre-dose[13]			X	X		X		X	X			X	See Section 8.3.3 for more information
ECG: triplicate reading pre-dose		X											See Section 8.3.3 for more information
ECG: single reading post-dose at 5, 7, 8 and 9 h		X						X[6]					See Section 8.3.3 for more information
Confirmation of PONCBP (female participants)	X												See Section 10.4.1.1 for more information
Hepatitis B and C serology	X												If test result available from within 3 months before first dose of study intervention, testing at screening is not required. See Section 8.3.4 for more information
Hematology/Chemistry/Urine	X	X		X		X		X	X	X	X	X	See Section 8.3.4 for more information
Fasting lipids and glucose (minimum 8 h)[7]		X							X			X	See Section 8.3.4 for more information
Lymphocyte T-cell subsets (CD4/CD8)	X								X				See Section 8.3.4 for more information

Procedure[1]	Screening[2] (7-14 days before Day 1)	Study Intervention Period Days 1-7							Post-Study Intervention Follow-up Days 8-21			Follow-up/ED[15]	Notes ED = early discontinuation/withdrawal
		Day 1	Day 2	Days 3 and 4 1 clinic visit and 1 virtual[3]		Days 5 and 6 1 clinic visit and 1 virtual[3]		Day 7	Day 8	Day 14 (+/- 1 day)	Day 21 (+/- 1 day)	Day 25 (+/- 1 day)	
		Clinic visit 1	Clinic visit 2	Clinic visit 3	Virtual[14]	Clinic visit 4	Virtual[14]	Clinic visit 5	Clinic visit 6	Clinic visit 7	Clinic visit 8	Clinic visit 9	
Syphilis RPR	X												See Section 8.3.4 for more information
Plasma for storage[8]		X	X	X		X		X	X	X	X	X	See Section 8.3.4 for more information
IWRS (RAMOS NG) activity[9]	X	X	X										See Section 6.3 for more information
Optional genetic sample		X											A separate genetics ICF is required
Observed administration of study intervention		X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]					See Section 6.1 for more information
Observed dosing with cART, and eCRF completion[11]									X	X	X	X	See Section 6.1 for more information
AE review		←	—	—	—	—	—	→	→	→	→	→	See Section 10.3.7 for more information
SAE review	←	—	—	—	—	—	—	→	→	→	→	→	See Section 10.3.7 for more information
Concomitant medication review	←	—	—	—	—	—	—	→	→	→	→	→	See Section 6.9 for more information
Serial PK sampling[12]		X						X					See Section 8.5 for more information
Single pre-dose PK sample[13]			X	X		X		X	X	X	X	X	See Section 8.5 for more information

The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
The CA and IEC will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the CA and the IEC before implementation.

1. Order of procedures (pre-dose): C-SSRS – ECG – Vital Signs – Blood Draws to allow the blood draw to occur as close as possible to the nominal time (See Section 8.5 for further information regarding order of blood draw and ECG during Clinic Visits 1 and 5 [Study Days 1 and 7]).
2. Participants will be randomized within approximately 7 to 14 days of the start of Screening but may be extended up to 28 days maximum. Screening laboratory assessments may be performed at the local laboratory in exceptional circumstances, if this more readily facilitates evaluation of the eligibility of potential study participants. The Investigator will review the local laboratory reports, confirm eligibility and document this in the eCRF. At the Screening site visit, the scheduled laboratory assessments should also be collected for analysis by the central laboratory.
3. Participants who pass screening will be required to attend 9 in-clinic outpatient visits. Flexibility is offered for Clinic Visits 3 and 4 which may take place on either Study Day 3 or Day 4 (Clinic Visit 3), or on Study Day 5 or Day 6 (Clinic Visit 4), with a virtual visit to be conducted on the non-clinic day. The visit schedule for each participant will be pre-planned to be sure weekend, work schedules and clinic hours are appropriately considered. In particular, Clinic Visits 1 and 5 (Study Days 1 and 7) must be scheduled on days when participants and site staff will be able to complete serial PK sampling up to 12 h post-dose.
4. Genotypic/Phenotypic testing will be conducted on Day 1 and Day 8 samples, with samples collected at other visits tested as appropriate.
5. Complete Physical Exam performed at Screening and Clinic Visit 9. . At all other clinic visits perform a Brief Physical Exam including, at a minimum, assessments of the Skin, Heart, Lungs, and Abdomen (liver and spleen). Any abnormalities to be recorded as AEs. Height measured at Screening only, weight measured at all indicated visits.
6. ECG reading at 5, 7, 8 and 9 h post-dose on Day 7 applies to Part 1A and optional QD cohorts in Part 2 only.
7. Clinical chemistry includes a lipid panel (total cholesterol, HDL, LDL and triglycerides). Blood collection for Clinical Chemistry should be collected after a minimum of an 8 hour fast on Days 1, 8 and 25 for fasting lipid assessment.
8. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits. These samples will be used when needed, such as when samples are lost or where quantity is insufficient for testing. In the event samples are not used by study completion, they will be utilized for additional research on antiretroviral resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing).
9. Log in to RAMOS NG at Screening to complete registration for participant ID assignment. Register any screen fails in RAMOS NG. Log in to RAMOS NG on Day 1 (Visit 1) and for Part 1A and optional QD cohorts in Part 2 on Day 2 (Visit 2) to dispense blinded study treatment. Subsequently log-in to RAMOS NG for study treatment supply as needed. If a participant is discontinued from the study early, log in to RAMOS NG to record the discontinuation.
10. CCI [redacted]
11. Observed dosing with cART is required at Day 8. At subsequent study visits, observed dosing is optional, however, at visits from Day 8, the investigator must document whether all prescribed cART doses were taken, or to document any missing doses as appropriate.
12. Serial Plasma VH3739937 PK samples will be collected on Days 1 and 7 CCI [redacted], as outlined in Table 7 and Table 8 in Section 8.5. In Part 2, QD cohorts will have the same PK sample schedule as Part 1A and single doses cohorts the same as Part 1B.
13. For single dose cohorts in Part 1B and optional Part 2, timepoints listed as pre-dose in the SoA will be time-matched to the time of dosing on Day 1.
14. HIV-associated conditions assessments, AE/SAE assessment, observed dosing with study intervention (Part 1A and optional Part 2A only), and concomitant medication review must be conducted with a participant during each day indicated. On the days when the participant does not come to the clinic (Study Day 3 or 4 and Day 5 or 6 as arranged with the participant), these assessments can be done via phone, preferably via a visual method (as locally permitted) of Skype, Facetime, WhatsApp, et. al.

15. Early discontinuation assessments to be performed if a participant withdraws early from study. Final follow-up visit will be approximately 18 days post last dose when it is estimated that the VH3739937 plasma concentrations are expected to be below the limit of quantification.

2. INTRODUCTION

2.1. Study rationale

The inhibition of maturation and release of HIV-1 is a novel target for drug development, distinct from viral protease, reverse transcriptase and integrase. There are no MIs approved for the treatment of HIV infection. VH3739937 is a MI that displays in vitro evidence of low nanomolar potency against multiple HIV-1 Gag polymorphisms and a broad spectrum covering multiple HIV-1 subtypes, supporting compound development.

Study 212580 is a POC, randomized, double blind study to characterize antiviral activity, safety/tolerability, PK, and the relationship between PK and antiviral activity of VH3739937 administered orally CCI [redacted], in HIV-1 infected treatment-naïve adults. The purpose of this study is to inform further clinical development of VH3739937. CCI [redacted]. This study will facilitate an understanding of the antiviral activity of VH3739937 CCI [redacted] and provide information on the safety profile, while limiting the exposure of HIV-1 infected participants to monotherapy with VH3739937 therefore reducing the likelihood of development of viral resistance.

2.2. Background

Infection with HIV-1 continues to be a serious health threat throughout the world, with approximately 1.2 million in the US and approximately 38.4 million infected individuals worldwide at the end of 2021 respectively, with approximately 1.5 million new HIV infections recorded in 2021 [UNAIDS, 2022]. Chronic exposure to cART has identified ARV-associated long-term toxicities (e.g., CNS or 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. There is still an on-going need for new ARV agents with improved safety and tolerability profiles with limited potential for drug-drug interactions for PLWH in particular as the population living with HIV ages. In this environment, medicines with novel mechanisms of action that can be used as part of the preferred cART regimen have an important role to play. However, any new oral ARV agent must be safe and effective, ideally provide a high barrier to resistance, have low toxicity, have minimal drug-drug interactions, and a desirable frequency of administration.

Currently no HIV-1 MI has been approved by a regulatory authority for treatment of HIV-1 infection, although several early phase studies of other MIs (bevirimat,

GSK2838232, GSK3532795 and GSK3640254) have been conducted [Martin, 2008; Morales-Ramirez, 2018; DeJesus, 2020; Dicker, 2022; Spinner, 2022)]. The MI under evaluation, GSK3739937 (also known and hereinafter referred to as VH3739937), has the potential to meet the requirements for a new ARV agent. CCI [redacted]

The clinical development of VH3739937 is on-going. Study 212548 was a FTiH study of oral formulation of VH3739937 investigating the safety, tolerability, and PK of single and repeated escalating doses in healthy participants. CCI [redacted] Study 212548 has shown VH3739937 to be generally well-tolerated in healthy participants and has demonstrated a PK profile suitable for progression to HIV-1 infected TN participants in this Phase 2a POC, 7-day monotherapy study CCI [redacted]

Data from these studies will be utilized to support future clinical development of VH3739937.

2.2.1. Key Clinical Safety and PK Data in Study 212548

2.2.1.1. Safety

In the FTiH study (212548) in healthy participants, VH3739937 PiB formulation following a moderate fat meal was observed to be safe and well tolerated. There were no Grade 3 or Grade 4 AEs, no SAEs or deaths, with the exception of 1 Grade 4 AE (transaminase elevation) in a participant randomised to receive PBO in Part 1 (SAD). Overall, the majority of AEs observed were Grade 1. No participant discontinued study due to an AE considered related to VH3739937 and no participant met a QTc study discontinuation criterion. Overall, the most commonly reported System Organ Classes for AEs were Gastrointestinal (abdominal pain, constipation and diarrhea) and General Disorders and Administration Site Conditions. The incidence of AEs considered related to the study drug was low and the majority of the study drug-related AEs were in the GI system-organ class. There were no clinically significant changes in clinical chemistry or hematology laboratory parameters, nor in vital signs, in participants who received VH3739937. There were no abnormal clinically significant arrhythmias or QTcF prolongations (values >500 msec) in the SAD, MAD and RBA / FE cohorts.

A regression analysis of time-matched change from baseline in QTcF and VH3739937 plasma concentration did not indicate a significant increase in change from baseline QTcF as concentration increases in either the SAD or MAD. A more robust cardiodynamic analysis is ongoing and is planned to be available prior to the start of this POC study; any clinically significant results will be sent to sites and ECs as a note to file. Full details are provided in the VH3739937 IB [GSK document No.: RPS-CLIN-017061].

2.2.1.2. Pharmacokinetics

CCI [redacted]

2.2.1.3. Summary

In summary, Study 212548 has shown VH3739937 to be generally well-tolerated in healthy volunteer participants and has demonstrated a PK profile suitable for progression to HIV-1 infected TN participants in this Phase 2a POC 7-day, monotherapy study. CCI [redacted]

2.3. Benefit/risk assessment

Based upon pre-clinical studies and clinical studies of prior Mis (GSK3532795 and GSK3640254 – both terminated in Phase 2b after reaching their Week 24 primary endpoint) the potential risks are GI intolerability (e.g., abdominal pain and diarrhea), gastric toxicity (effects on parietal cells and chief cells), prolongation of QTc, skin and subcutaneous tissue disorders (maculopapular rash), neuropsychiatric safety, and treatment emergent virologic resistance. These are described in detail in the table below.

To ensure the overall safety of participants (including the risks described above), 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 VH3739937 may be found in the IB [GSK document No.: RPS-CLIN-017061].

The Sponsor has assessed this study for any risks that may be posed to participants. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of FDA and the EMA guidance on strategies to identify and mitigate risks for clinical studies with IMPs [EMA, 2017].

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [VH3739937]		
Cardiovascular (QT prolongation)	**Preclinical**: • Weight of evidence from preclinical in vitro and in vivo cardiovascular studies suggests a low potential for QT prolongation in humans at exposures up to the highest predicted median maximum observed concentration (Cmax) of CCI µg/mL (CCI µg/mL free) with no CV effects observed in a dog CV study at exposures of CCI µg/mL (CCI µg/mL free). or in the 4-week dog study up to CCI µg/mL CCI µg/mL free). **Clinical**: • In the 212548 FTiH study of VH3739937, no clinically significant elevations of QTcF were observed (nor did any patient meet QT stopping criteria). **Clinical prior MI**: • In a thorough QT study, supratherapeutic dose of GSK3640254 500 mg has shown to significantly prolong QTc interval 10.6 msec (clinically important threshold is 10 msec).	• Protocol exclusion criteria based on ECG parameters and cardiac medical history (see Section 5.2). • ECGs and frequent clinical and vital sign evaluations will be collected during the study (see Section 1.3). • As noted in Section 7, if a clinically significant finding is identified (including but not limited to changes from baseline in QTcF) after enrolment, 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal intolerability	**Preclinical**: • Clinical signs indicative of gastrointestinal intolerability (sporadic vomiting and abnormal faeces) occurred mainly in dogs at ≥30 mg/kg/day. **Clinical**: • In the 212548 FTIH study, Gastrointestinal AEs: diarrhea, constipation and abdominal pain were reported, the majority were considered grade 1. No GI event led to discontinuation. For further detail, please see IB [GSK document No.: RPS-CLIN-017061]. **Clinical prior MI**: • GI events (abdominal pain, diarrhea and nausea) have been added as Adverse Drug Reactions to the non-EU Reference Safety Information of the GSK3640254 IB [GSK document No.: RPS-CLIN-045350]. Gastrointestinal intolerability is categorized as an identified risk for GSK3640254.	• Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms • Study participants will undergo physical examinations, laboratory testing and continuous evaluation for adverse events. See stopping criteria based upon the incidence and intensity of treatment-emergent AEs (Section 7.1.3). Additionally, a GI intolerability evaluation and monitoring plan is available to guide the investigator should GI AEs emerge (see Section 8.3.8).
Gastric toxicity	**Preclinical**: • Dose and duration-dependent microscopic changes (single-cell necrosis and decreased cellularity of parietal cells and/or	• There is no specific clinical approach for evaluating gastric toxicity in Study 212580. However, based on nonclinical data, and the highest predicted clinical exposure in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	chief cells), were observed in the glandular stomach of rats and dogs dosed with GSK3739937 from 7 days to 4 weeks duration. The stomach findings in the definitive 4-week studies were minimal to mild in nature and shown to be reversible in both rats and dogs with a NOAEL for rats of 10 mg/kg/day and the LOAELs in rats and dogs, of 40 and 3 mg/kg/day, respectively (1.4X and 0.7X the highest median predicted clinical AUC0-24 CCI in this clinical study, respectively). A NOAEL for microscopic changes in the stomach of dogs was not identified. **Clinical prior MI:** • GSK3640254 and GSK3532795: Toxicity findings of single-cell necrosis and decreased cellularity of parietal cells and/or chief cells in the stomach were present in preclinical species with GSK3640254 and GSK3532795. These findings were reversible. • GSK3640254: Phase 2b Study 208379 included a gastric sub-study (n= 17). Gastric biopsies (2 in greater curvature and 2 in transitional zone) were taken at Day 1 and Week 24 and evaluated microscopically:	Study 212580 at approximate parity to the LOAEL in rats and dogs, any changes to parietal or chief cells that may occur in the stomach of humans are expected to be minimal to mild, asymptomatic and reversible following up to 28 days of exposure.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	gastric biomarkers (gastrin, pepsinogen I and II) were obtained in all participants in the study (n = 17). At Week 24, there was no evidence of dose-dependent induction of gastric pathology by GSK3640254, findings were within normal limits including spontaneous mild reactive gastritis. There was no evidence of significant deleterious pathology including metaplasia or dysplasia. Serum gastrin levels were consistent with normal acid secretion from gastric parietal cells and there was no clear evidence of parietal cell loss following drug treatment	
Neurologic/psychiatric safety	**Preclinical:** • CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration. CNS penetration studies with GSK3739937 have not yet been performed. **Clinical:** • In the FTIH and RBA study with VH3739937 no psychiatric AEs have been reported. The most common nervous system disorder was headache. See VH3739937 IB for summary of nervous system AEs [GSK document No.: RPS-CLIN-017061	• Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment and the C-SSRS) for participants in the study. • Continuous evaluation for adverse events during their participation in the trial including direct AE inquiry. • Participants will have C-SSRS assessments regularly throughout the study. Ultimately, in the event of a new onset suicidality ideation or behavior, as determined by the investigator (in consultation with psychiatry, as needed), the participant will discontinue from the trial and the Investigator will

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical prior MI: • Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. • Neuropsychiatric adverse events were reported infrequently in the GSK3640254 program and were mostly grade 1; Psychiatric SAEs have been reported in the Phase 2b studies, none were considered related and all cases had either baseline psychiatric history (not disclosed during screening) or confounded factors which were the most likely cause of the event. For the Phase 2b study evaluating GSK3640254/DTG relative to DTG/3TC, the rates of nervous system AESI were 9-23% relative to 10%, respectively. The psychiatric system AESI were 0-10% relative to 14%, respectively. • For the Phase 2b study evaluating GSK3640254 relative to DTG (both in combination with 2 NRTI), the rates of nervous system AESI were 9-17% relative to 8%, respectively. The psychiatric system	arrange for urgent specialist psychiatric evaluation and management. • Guidance for the management of emergent psychiatric symptoms are available (see Section 8). • There are clinical stopping criteria based upon intensity of treatment-emergent psychiatric AEs (see Section 7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	AESI were 3-7% relative to 6%, respectively.	
Skin and subcutaneous tissue disorders	**Clinical:** • In the 212548 FTIH study, no adverse events of rash considered by the investigator as attributable to VH3739937 were reported. • In the FTIH and RBA study with GSK3739937, skin disorders AEs (primarily dermatitis due to ECG leads) were reported, the majority of which were mild (Grade 1) and not considered related to study medication. **Clinical prior MI**: • Across GSK3640254 clinical studies, AEs leading to discontinuation have included urticaria and maculopapular rash. • Rash has been added as Adverse Drug Reactions to the non-EU Reference Safety Information of the GSK3640254 IB [GSK document No.: RPS-CLIN-045350]. Skin and subcutaneous tissue disorders is categorised as an identified risk for GSK3640254.	• Participants with a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation are excluded. • Study participants will undergo continuous evaluation for adverse events supplemented by physical examinations. • See clinical stopping criteria based upon the intensity of treatment-emergent skin and subcutaneous tissue disorder AEs and laboratory abnormalities (Section 7.1.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
HIV Resistance to VH3739937	**Clinical:** • There is an intrinsic risk of resistance (genotypic changes or decreased phenotypic susceptibility) to any developmental ARV – particularly when given in monotherapy **Clinical prior MI**: • Data from the GSK3640254 Phase 2a POC study showed a decline in HIV-1 RNA and a variable PK/PD relationship. However, 4 of 6 participants receiving GSK3640254 CCI [redacted] had treatment emergent genotypic changes associated with resistance to maturation inhibitors observed CCI [redacted] However, no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase, protease, integrase) was observed and there is no known cross-resistance between MIs and other classes of ARVs. Genotypic analysis of samples at Study Day 8 or 9 revealed no treatment emergent resistance.	• This Phase 2a study is limited to 7 days of monotherapy. Doses of VH3739937 in all active therapy Cohorts 2 to 4 were selected to ensure that from Day 1 throughout the dosing period, at least 95% of the study participants achieve plasma concentrations above 3-times the protein binding-adjusted EC_{90} (3xPBA-EC_{90}) for a panel of HIV-1 to reduce the risk of emergent MI drug resistance. See IB [GSK document No.: RPS-CLIN-017061]. • There are no commercially available/approved MIs nor is there evidence of cross-class resistance (e.g., as occurs for protease inhibitors). Therefore dosing with VH3739937 will not impact selection of effective ART at the completion of the study. • Study conduct will ensure strict adherence to criteria addressing concurrent medications
Study Procedures		
Lead irritation from ECG leads	• In the event of irritation from ECG leads, up to 2.5% topical hydrocortisone may be used at the discretion of the investigator	• See Section 6.9 for further detail on permissible concomitant medications

2.3.2. Benefit assessment

This study in HIV-1 infected, TN and otherwise healthy participants is a short-term monotherapy design. There is no expected longer-term anti-HIV benefit to administration of VH3739937 during this study; however, participants will transition to standard of care cART on study Day 8. Potential delays in initiating combination ART as a result of participating in this study are expected to be short and are not expected to have any clinically relevant impact upon study participant outcomes.

2.3.3. Overall benefit-risk conclusion

Given the preclinical and clinical profile to date, the overall risk to HIV-1 infected, TN and otherwise healthy participants at the proposed VH3739937 doses, for 7 days, is predicted to be low and manageable. Mean exposures at the highest dose to be studied are not projected to exceed mean LOAEL values obtained in 28-day toxicology studies, further reducing potential risk.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with VH3739937 are justified by the anticipated benefits that may be afforded to participants with HIV-1 infection.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1. Objectives and Endpoints

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of VH3739937 in HIV-1 infected TN participants during 7 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 RNA through Day 8
Secondary	
• To assess the safety and tolerability of VH3739937 when administered as monotherapy over 7 days in HIV-1 infected TN participants	• Incidence of SAEs, Deaths and AEs leading to Discontinuation through Day 8
• To characterize the pharmacokinetics of VH3739937 in HIV-1 infected TN participants	VH3739937 PK parameters : Following QD dosing: • Day 1: Cmax, tmax, C24 and AUC(0-24) • Day 7: Cmax,ss, tmax, C24,ss and AUC(0-24),ss Following single dose: Cmax, tmax, AUC(0-168) and C168
Exploratory	
• To assess the safety and tolerability of VH3739937 when administered as monotherapy over time in HIV-1 infected TN participants	• Incidence of AEs and severity of AEs through Day 25 • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters (consisting of total and direct bilirubin, ALT, ALP and AST)
• To assess the occurrence of Gag treatment emergent mutations or substitutions after 7 days of monotherapy with VH3739937	• Genotypic assessment to detect any change in the Gag gene sequence from Day 1 to Day 8
• To assess the immunologic effects of VH3739937 when administered over 7 days in HIV-1 infected adults	• Change from baseline in CD4+ T-cell count through Day 8

• To characterize the pharmacokinetics of VH3739937 in HIV-1 infected TN participants	Additional VH3739937 PK parameters: • Following QD dosing (Day 7 only): CL/F, V/F and t1/2 will be determined if possible • Following single dose: AUC(0-24) and C24, In addition, AUCinfinity, CL/F, V/F and t1/2 will be determined where possible
• To explore relationship(s) between plasma concentrations of VH3739937 and pharmacodynamic, efficacy and/or safety endpoints.	• Appropriate VH3739937 PK parameters with pharmacodynamic, efficacy and/or safety endpoints (e.g., change in plasma HIV-1 RNA, CD4+ cell count etc) may be explored as deemed appropriate
Note: Other exploratory objectives and endpoints may be specified in the SAP.	

CCI

[redacted]

CCI

[redacted]

4. STUDY DESIGN

4.1. Overall design

This is a Phase 2a, POC, multi-center, randomized, double-blind (Sponsor-unblinded), placebo-controlled, adaptive clinical study to evaluate the antiviral effect, safety, tolerability, and PK/PD of orally administered VH3739937 over 7 days initially in approximately 20 TN HIV-1 infected adults who are termed "participants" in this study. Optionally approximately 20 further participants may be enrolled in Part 2. Please see Section 9 for statistical considerations and Section 9.5 for further detail on definition of screen failures and non-evaluable participants.

All participants will be screened for eligibility preferably within approximately 7 to 14 days before being randomized into a 7-day study intervention period. The screening period may be extended to 28 days to allow, at a minimum, receipt of all screening results and/or to accommodate scheduling.

If participants prematurely discontinue the study for non-safety reasons, additional participants may be recruited with randomization and assignment to the same cohort (to ensure a minimum of 5 evaluable participants in each of cohorts 2 to 4 and optional cohorts 5, 6 and 7) at the discretion of the Sponsor in consultation with the Investigator.

Participants will not be replaced if the reason for discontinuation is the original participant meeting stopping criteria (with the exception of moderate to severe COVID-19 infection).

This study will be conducted in two parts. In the first part (Part 1), approximate 20 TN HIV-1 infected adults will be randomized to one of 4 cohorts as described in the table immediately below. Part 2 of the study is optional and will be adaptive; the dose(s) and frequency of administration of VH3739937 are to be determined based on a planned interim analysis by the Sponsor study team using available, unvalidated, preliminary clinical data from Part 1. If Part 2 is conducted, it will include up to 3 additional cohorts, where up to 6 participants would receive VH3739937 in each cohort; up to 2 further participants would also be enrolled into Cohort 1, to receive placebo. Part 2 QD cohorts (Part 2A) will follow the same schedule as those in Part 1A, and single dose cohorts (Part 2B) will follow the same schedule as for Part 1B. If both QD and single dose cohorts are included in Part 2, an additional Cohort 1 participant will be enrolled into each of Parts 2A and 2B.

Part	Cohort Number	Number of Participants	Intervention
1A	1	1	[1] Placebo CCI [redacted]
	2	6	VH3739937 CCI [redacted]
	3	6	VH3739937 CCI [redacted]
1B	1	1	[1] Placebo CCI [redacted]

Part	Cohort Number	Number of Participants	Intervention
	4	6	VH3739937 CCI [redacted]
2A and/or B	1	Up to 2	[1]Placebo CCI [redacted]
	5-7	Up to 6 each	Number of Cohorts, dose and dose frequency to be decided based on Part 1 Cohort data

[1] For placebo tablets please see Section 6.1 for further detail.

In Part 1, 3 cohorts of approximately 6 participants will receive active doses of VH3739937 and one cohort of approximately 2 participants will receive placebo CCI [redacted] Most participants will be randomized within approximately 14 days of the start of Screening; up to 28 days maximum will be allowed. Participants will receive SOC cART selected and prescribed by the Investigator starting on Day 8 after all study procedures and assessments have been performed. Participants will be followed for on study assessments until Day 25, 18 days after the last dose of study intervention. The SOC cART will be sourced as per local requirements.

CCI [redacted] Please see Section 4.3 for further detail on justification of the planned dose levels of VH3739937.

Following Screening, the study requires a total of 9 in-clinic visits with flexibility of up to 2 virtual visits offered, one on either of Day 3 or Day 4 and one on either of Day 5 or Day 6. For all participants in Part 1, dose administration on Day 1 will occur at the study site. For participants in Part 1A only, an appropriate number of bottles will be dispensed on Day 2, with a supply sufficient to cover Days 2 to 7 of the treatment period. The bottles will contain CCI [redacted] either the active (VH3739937) dose or placebo and will be dispensed in a manner ensuring the blinding of the participant and site staff. Participants will be provided with a dosing card with instructions on the number of CCI [redacted] to take from each bottle per day. Participants will bring the bottles of study intervention to each clinic visit through to Day 7, so that administration of study intervention can be observed in the clinic after the study procedures have been performed.

Part 2 may evaluate further CCI [redacted] doses CCI [redacted]

CCI [redacted]

Study treatments will be administered near the same time each morning, within a 2-hr window (e.g., 9 am +/- 2 hrs).

On the days when participants in Part 1A (and optional Part 2A) self-administer the study treatment during a virtual visit, observed dosing with a site staff member may be achieved as locally permitted using various forms of video calling (when at all possible) such as FaceTime, Skype, WhatsApp. Virtual visits for Part 1B (and optional Part 2B) may be conducted by standard telephone call, as no observed dosing is required.

The post-dosing of study intervention follow-up period will consist of 4 in-clinic visits on Days 8, 14, 21 and 25. On Day 8, participants will start cART selected and prescribed by the Investigator and sourced as per local requirements, immediately following the completion of Day 8 study assessments. PK and safety assessments will be taken approximately 24 h post last dose (Day 8) until the final Follow Up visit planned approximately 18 days post dose at Day 25, when it is estimated that VH3739937 plasma concentrations are expected to be below the limit of quantification. At this Day 25 visit, HIV-1 RNA, PK and safety (e.g., to follow any AEs to resolution), will be assessed as shown in the SoA (Section 1.3).
Total duration of study participation is approximately 32 to 53 days based on the following:

- 7 to 14 days, with a maximum of 28 days permitted for screening/qualification period
- 7 days for treatment with the study intervention and assessment at all planned visits
- 18 days for post-study intervention follow up visits including the final follow up visit. Participants will take cART throughout this period.

4.2. Scientific rationale for study design

This Phase 2a study of VH3739937 will be conducted in HIV-1 infected, TN participants to decrease the possibility of participants experiencing viral resistance to VH3739937. Dosing with VH3739937 will be limited to 7 days of monotherapy as an additional measure to decrease the probability of development of resistance to VH3739937.

CCI [redacted]

CCI [redacted] On Day 8, all participants will switch to combination antiretroviral therapy selected by the investigator and remain on study for evaluation based on the elimination of the majority of VH3739937 which is anticipated to be achieved approximately 18 days after the last dose of VH3739937. There are no commercially available/approved MIs nor is there evidence of cross-class resistance (e.g. as occurs for protease inhibitors) therefore dosing with VH3739937 will not interfere with selection of the cART regimen selected by the investigator on Day 8 and any subsequent regimen following completion of the study.

The justification for the use of a placebo control allows for blinded assessment of relationship to a treatment emergent adverse event. One placebo cohort of 2 participants will facilitate blinded assessment of safety and tolerability. Since Investigators and participants will be blinded, any safety event (AE, lab abnormality, ECG abnormality, etc) will be evaluated and managed in the same fashion. Further, there is no evidence that delaying initiation of cART by 7 days in a TN study participant will adversely impact the short and long term clinical outcomes following the initiation of cART [Egger, 2002].

4.2.1. Participant input into design

This is the first study of VH3739937 in people living with HIV-1. Participants were not engaged in development of the study design which is consistent with other Proof of Concept Phase 2a studies of antiretroviral therapies.

4.3. Justification for dose

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

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

Part 2 of the study is optional. Completion of the study at the end of Part 1 will not be considered an early termination.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

Age

1. Participant must be 18 to 65 years of age inclusive at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy (other than HIV infection) as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Screening CD4+ T-cell count ≥200 cells/mm3
4. Documented HIV infection and Screening plasma HIV-1 RNA ≥3000 (≥3.48log10) and <1,000,000 (<6.0log10) copies/mL. A single repeat of this test is allowed within a single Screening period to determine eligibility.
5. Positive HIV antibody test
6. Treatment-naïve: No ARVs (in combination or monotherapy) received after the diagnosis of HIV-1 infection.

Weight

7. Body weight ≥50.0 kg (110 lbs.) for men and ≥45.0 kg (99 lbs) for women and BMI for all participants within the range 18.5-35.0 kg/m^2.

Sex and Contraceptive/Barrier Requirements

8. All participants in the study should be counseled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

   *NOTE: There are no contraceptive requirements for participants who were male at birth.

   Participants Female at birth:

   A participant who was female at birth is eligible to participate if they are a PONCBP (see Appendix 4).

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

Informed Consent

9. 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 and stated in this protocol.

Other Inclusions

10. Participant must be willing and able to start cART as selected with the Investigator on Study Day 8 (except in the case of early termination, clinically relevant AE/SAE, lab abnormality, the withdrawal of consent, lost to follow-up, etc., where circumstances could dictate otherwise).

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 during the study;
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; or other localized malignancies require agreement between the investigator and the study medical monitor for inclusion of the participant prior to randomization. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days of study drug administration or anticipated need for such treatment within the study;
3. 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 C-SSRS. Participants' history of suicidal behaviour and/or suicidal ideation should be considered when evaluating for suicide risk;
4. 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.
5. 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), may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant;
6. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);
7. Participants with 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;

8. A pre-existing condition, in the opinion of the Investigator or Medical Monitor, that could interfere with normal gastrointestinal anatomy or motility (e.g., GERD, gastric ulcers, gastritis, inflammatory bowel disease), hepatic and/or renal function, that could interfere with the absorption, metabolism, and/or excretion of the study interventions or render the participant unable to take oral study treatment;
9. Myocardial infarction, acute coronary syndrome, unstable angina, stroke, transient ischemic attack, or intermittent claudication in the past 3 months;
10. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome or sudden cardiac death. Any significant arrhythmia or ECG finding which, in the opinion of the Investigator or Medical Monitor, will interfere with the safety for the individual participant;
    - Examples of ECG findings include symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained VT or sustained VT, AVB Mobitz Type II, or third degree AVB.

Prior/Concomitant Therapy

11. Prior exposure to a MI
12. Treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (such as hydroxyurea or foscarnet) within 30 days of study drug administration. If patients received ARV(s) for PrEP inadvertently after their diagnosis of HIV-1, they cannot screen for this trial until 5 half-lives have elapsed.
13. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing. Specific medications listed in Section 6.8 may be allowed;
14. History of sensitivity to any of the study medications, or their components or drugs of their class, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation. Participants who require concomitant medications known to be associated with a prolonged QTc;
15. Treatment with any of the following agents within 28 days of Screening: radiation therapy, cytotoxic chemotherapeutic agents, any systemic immune suppressant;
16. Participants receiving any protocol-prohibited medication and who are unwilling or unable to switch to an alternate medication;

Prior/Concurrent Clinical Study Experience

17. The participant has received an investigational HIV vaccine (immunotherapeutic or immunomodulatory);

18. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of study intervention;

Diagnostic Assessments

19. Untreated syphilis infection [positive RPR at screening] without documentation of treatment. Participants who have successfully completed treatment at least 7 days previously are eligible if recruitment is open;
20. QTc >450 msec or QTc > 480 msec in participants with bundle branch block
21. Exclusion criteria for screening ECG (a single repeat is allowed in some instances for eligibility determination):

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

    Notes:

    - A heart rate <50 or >110 bpm is exclusionary and cannot be rechecked to determine eligibility.
    - A heart rate from 101-110 bpm can be checked by a single repeat ECG or by vital signs within 30 minutes to verify eligibility.
    - The QTc is the QT interval 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 an individual participant in this study. The Investigator's or Medical Monitor's over-read can supercede that of the machine at any time.
22. Presence of HBsAg or HBcAb at screening

    Note: Evidence of HBV infection based on the results of testing at Screening for HBsAg:

    - Patients who are negative for HBsAg should also be tested for anti-HBc, anti-HBs and HBV DNA and excluded according to the following algorithm:
        - Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded
        - 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.

    Note: HBV DNA testing will only be performed during screening and prior to randomisation for participants with positive anti-HBc and both negative HBsAg and anti-HBs (past and/or current evidence).
23. 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 (central lab will automatically reflex to HCV RNA on positive HCVAb)

24. Any Grade 2-4 laboratory abnormality at Screening, with the exception of CPK and lipid abnormalities (e.g., total cholesterol, triglycerides, etc), ALT (described below) and eGFR, will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any lab abnormality is allowed within a single Screening period to determine eligibility;
25. ALT ≥ 1.5 x ULN or total bilirubin ≥1.5xULN. A single repeat of ALT and / or bilirubin is allowed within a single Screening period to determine eligibility;
26. Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude participation in the study of an investigational compound;
27. eGFR of < 50 mL/min/1.73 m^2 via CKD-EPI 2021 method;
28. Any positive result for illicit drug use (e.g., cocaine, heroin) at Screening. A positive screen for marijuana / THC is not exclusionary, see Section 5.3.2 for guidance to be given to the participant.

Other Exclusion Criteria

29. Regular use of drugs of abuse
30. Sensitivity to heparin or heparin-induced thrombocytopenia

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

Participants will be required to fast for at least 8 h [overnight] prior to the morning check-in at clinic visits on Days 1-8 and Day 25 in Part 1A (and optional Part 2A) and Days 1, 8 and 25 in Part 1B (and optional Part 2B). Procedures will be performed in the following order: C-SSRS, ECG, Vital Signs and Blood Draws in a fasted state. On days when participants take the study intervention, each dose will be taken with approximately 240 mL (8 ounce) water following ingestion of a moderate calorie and fat meal, to be completed within approximately 25 minutes just prior to dosing, with dose administration to occur within 5 minutes of completion of meal consumption. This includes the virtual visits where participants must have completed their meal within approximately 25 minutes of their scheduled call with site staff, with dose administration to occur within 5 minutes of completion of meal consumption.

Refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 3 days before the start of study intervention until Day 8.

5.3.2. Caffeine, alcohol, and tobacco

During the study alcohol consumption will be limited to the following: An average weekly intake of <14 drinks for participants assigned as male at birth or <7 drinks for participants assigned as female 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.

No alcohol will be consumed on the in-clinic serial PK days (Day 1 and, if applicable, Day 7) until after the final assessment of the day and release from the clinic.

Only clinically minor to moderate use (as determined by the Investigator) of tobacco products will be allowed during study participation, with extremely limited use on the in-clinic serial PK days (Day 1 and, if applicable, Day 7).

Participants should refrain from the use of marijuana during the treatment period.

5.3.3. Activity

Participants will abstain from strenuous exercise during Days 1 to 8.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, information from any previous trials with the same IP, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if, in the opinion of the Investigator, the current clinical outlook of the participant is favorable for study inclusion.

Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be record in the participants' CRF/eCRF. All screening procedures should be repeated at the rescreening visit.

5.5. Criteria for temporarily delaying enrollment/randomization/administration of study intervention

Not applicable

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Table 4 Study Intervention(s) Administered

Intervention Label		
Intervention on Label:	VH3739937 CCI	Placebo to match VH3739937 CCI
Intervention Description	CCI	CCI
Type	Drug	Drug
Dose Formulation:	CCI	CCI
Unit Dose Strength(s)	CCI	N/A
Dosage Level(s):	Variable depending on dose	Variable depending on dose
Route of Administration	Oral	Oral
Dosing instructions:	CCI	
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Packaging and Labeling	Blinded Study Intervention will be provided in high-density polyethylene (HDPE) bottles which contain a desiccant. Each bottle will be labelled as required per country requirement.	Blinded Study Intervention will be provided in high-density polyethylene (HDPE) bottles which contain a desiccant. Each container will be labelled as required per country requirement.
Sourcing / Manufacturer	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Current/Former Name(s) or Alias(es)	GSK3739937	Not Applicable

6.2. Preparation, handling, storage, and accountability

The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

All study intervention 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.

The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.

A 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 ViiV Healthcare/GSK.

6.3. Assignment to study intervention

All participants will be centrally assigned to randomized study intervention according to a computer-generated randomization schedule provided by the Sponsor, using RAMOS NG. Before the study is initiated, the telephone number and call-in directions for RAMOS NG and/or the log-in information and directions for RAMOS NG will be provided to each site.

Participants will ideally be randomized within 14 days of the start of Screening; up to 28 days maximum may be allowed. In Part 1, 3 cohorts of approximately 6 participants will receive active doses of VH3739937 and 1 cohort of approximately 2 participants will receive placebo. As noted earlier, the dose(s)/frequency and exact arms/sample size for Part 2 are to be determined based upon a planned interim analysis of available preliminary unvalidated clinical data.

Study intervention will be dispensed at the study visits as summarized in the SoA.

Returned study intervention should not be re-dispensed to the participants.

6.4. Blinding

Emergency unblinding RAMOS NG	This is a double-blind study in which participants/care providers/investigators/outcomes assessors, etc. are blinded to study intervention. RAMOS NG will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' 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 may, at the investigator's discretion, contact ViiV Healthcare/GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, ViiV Healthcare/GSK must be notified within 24 h of this occurrence. The date and reason for the unblinding must be recorded. If the investigator is unable to access RAMOS NG, they can contact the GSK helpdesk based on the information provided in the pharmacy manual. A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

This early phase study of relatively small size will not use an external DMC. The ongoing monitoring of blinded study data including clinical safety, efficacy and PK data will be overseen by an experienced central ViiV Healthcare/GSK study team. This central study team will have access to unblinded data if indicated and, if appropriate, will discuss data in a blinded fashion when interacting with site staff. As a general principle during study

conduct, members of the ViiV Healthcare/GSK study team and other ViiV Healthcare/GSK staff will remain blinded unless unblinding becomes necessary.

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 eCRF.

ViiV Healthcare/GSK's Global Safety 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 ViiV Healthcare/GSK policy.

6.5. Study intervention compliance

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

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

When participants self-administer the study intervention at home, compliance with study intervention dosing will be assessed by observed dosing with a site staff member as locally permitted using various forms of video calling (when at all possible) such as FaceTime, Skype, WhatsApp. In addition, compliance with study intervention dosing will be confirmed by counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosing regimen should be recorded.

A record of the quantity of VH3739937 CCI and / or placebo dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded.

6.6. Dose modification

No dose modifications are permitted in this study.

6.7. Continued access to study intervention after the end of the study

Given the lack of longer-term clinical benefit (Section 2.3.2), ViiV Healthcare recognizes the balance between the need to conduct an early phase monotherapy clinical study (for the larger and long term unmet medical need) and the need for HIV-1 infected treatment

naïve patients to receive cART as soon as possible after diagnosis. To meet both needs, this study design is efficient in screening (shortest period: approximately 7 to 14 days) and the monotherapy treatment with VH3739937 (period: 7 days). On study Day 8, following the scheduled blood collection as per SoA, participants will commence cART selected and prescribed by the investigator and sourced as per local requirements. After this time, the investigator is responsible for ensuring that participants continue to receive cART, whether or not the Sponsor is providing reimbursement for post-study treatment.

The Sponsor recognizes some HIV-1 infected adults may encounter barriers to accessing cART. Where it has been determined by the Investigator to be an acceptable option, participants receiving study treatment will have the option (but are not required) to receive reimbursement from the Sponsor for locally marketed ARVs (after the completion of dosing and through the study final follow-up visit) for up to a maximum of 90 days. The selection of ARVs will be investigator-chosen based upon local standard of care.

6.8. Treatment of overdose

An overdose is any dose of study intervention given to a participant that exceeds the planned, randomized dose for an individual within a given dose group.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until VH3739937 can no longer be detected systemically (at least 18 days), as medically appropriate.
- Obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and concomitant 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 vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given at least 14 days prior to Screening. Please discuss with medical monitor if planned to give during this time.

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 enrolment 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.

6.9.1. Permitted Medications:

1. Acetaminophen/paracetamol at doses of ≤2 g/day or NSAIDs are permitted for use any time during the study and their use documented in the CRF.
2. In the event of irritation from ECG leads, up to 2.5% topical hydrocortisone may be used at the discretion of the investigator.
3. Any vaccine, including those available and approved for SARS-CoV-2 and other non-HIV vaccines should be administered at least 14 days prior to Screening. Please discuss with Medical Monitor if planned to give during the study period.
4. Other concomitant medications may be considered on a case by case basis by the investigator in consultation with the medical monitor if required.

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Participants must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the counter because of the potential for interactions between such treatments and the study medications.

6.9.2. Prohibited Medications and Non-Drug Therapies

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

- HIV immunotherapeutic / immunomodulatory vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered.
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited. This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to immunosuppressive effect; however, short treatment courses (e.g., 14 days or less) of oral prednisone/ prednisolone/methylprednisolone are allowed. Topical, inhaled or intranasal use of glucocorticoids will be allowed.
- Acetaminophen (paracetamol) cannot be used in patients with acute viral hepatitis [James, 2009].
- Participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives

(whichever is longer) before the start of study intervention until completion of the final visit on Day 25, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

- Narrow therapeutic index drugs that are substrates of P-gp or CYP3A are not permitted during study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of 10.1.

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of the study intervention. In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study (i.e., continue with study visits). See the SoA (Section 1.3) for data to be collected at the time of early discontinuation of study intervention (ED Visit). If the participant agrees, participants who discontinue study intervention should return to complete a follow-up visit approximately 18 days after their final dose of study intervention. Any new clinically relevant finding should be reported as an AE.

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

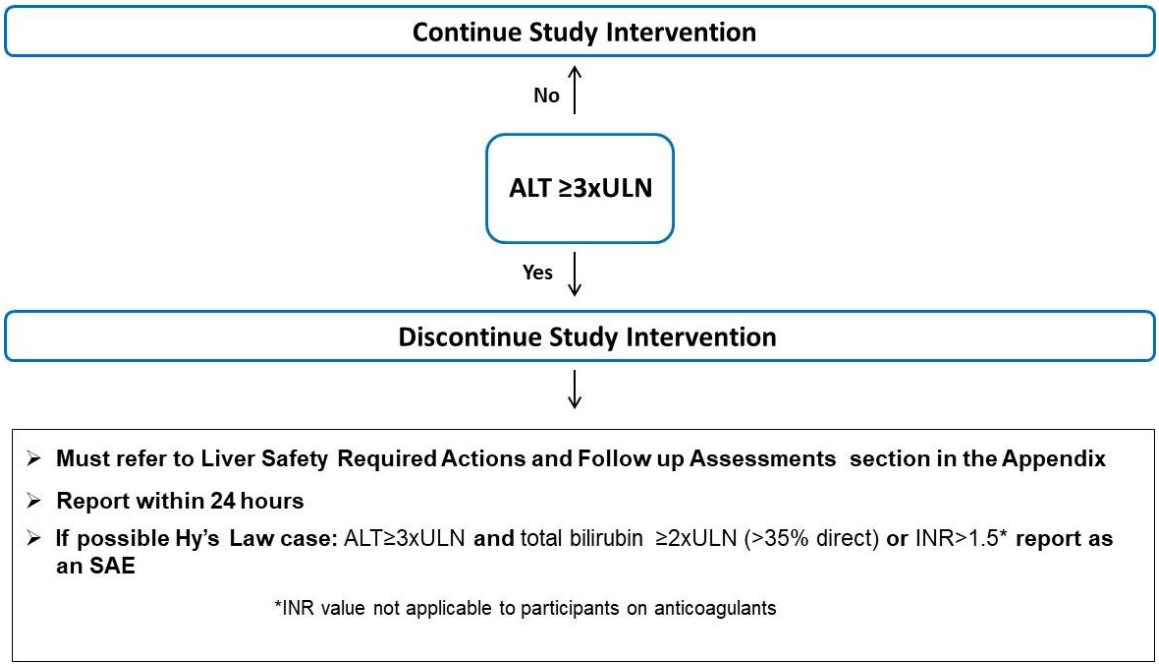
- Liver toxicity where stopping criteria specified in Liver Chemistry Stopping Criteria (Section 7.1.1) are met and no compelling alternate cause is identified;
- Cardiac Changes (e.g., QTc) (see Section 7.1.2)
- Rash criteria as described in Section 10.7 are met and no compelling alternate cause is identified.
- Grade 4 clinical AE (see Section 7.1.3 for further detail);

Pregnancy (intrauterine), regardless of termination status of pregnancy (see Section 8.3.5). **The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:**

7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Liver Chemistry Stopping Criteria Algorithm



Refer to Section 10.6 for required Liver Safety Actions and Follow-up Assessments

7.1.2. QTc Stopping criteria

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 the study intervention 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 QTcF correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study.

The Baseline QTcF should be based on average QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period from the Day 1 pre-dose ECG.

The average of triplicate ECG readings is the preferred method for confirmation of stopping threshold.

A randomized participant who develops an on-treatment QTcF >500 msec or an increase from baseline QTcF >60 msec should have two repeat unscheduled ECGs within 10 minutes. Using these triplicate ECGs, if the average QTcF >500 msec or an increase from baseline QTcF >60 msec, the participant will be withdrawn from the study. Finally, this participant should have repeated unscheduled ECGs until their QTcF measurement returns to their original averaged QTcF value at Day 1 pre-dose.

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

7.1.3. Individual Participant Laboratory Abnormality and Adverse Event Stopping Criteria

Investigators should make every effort to have a discussion with the Medical Monitor before the next dose to help assess if the study intervention should be stopped. Individual participant laboratory abnormality and AE stopping criteria for the study, as follows:

Adverse Event	• Any clinically significant AE deemed to require discontinuation of the IP • Any related Grade 3 or any Grade 4 rash • Grade 2 rash with evidence of systemic involvement • Grade 2 or higher rash with concurrent fever, AST/ALT elevation or eosinophilia prior to the follow up phase will be withdrawn from study intervention • Grade 3 or higher allergic reaction • 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 emergency specialist psychiatric evaluation/management • Any Grade 3 or higher AE related to study medication • Any Grade 4 AE or laboratory abnormalities (with the exception of an asymptomatic grade 4 cholesterol, triglyceride or CPK increase) • A participant meets the QTcF stopping criteria described in Section 7.1.2 • 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)

7.1.4. Temporary discontinuation

Withdrawal of study treatment, including any missed dose on Days 1 to 7 CCI [redacted], requires withdrawal from the study. See Section 7.2 for further detail.

7.1.5. Rechallenge

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

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an ED visit should be conducted together with a follow-up visit approximately 18 days after the last dose of study intervention, 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. A participant who is withdrawn from the study for any reason related to safety (listed in Section 7.1 or otherwise) will continue to be followed up to assess the outcome of the safety event that triggered discontinuation of study drug. If a participant is unable to return to the clinic for any reason, site staff are encouraged to contact the participant for assessment of AEs.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. 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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE Solicited AE
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver Event QTc Laboratory Abnormality
Physician Decision	Loss of ability to freely provide consent due to treatment of either a psychiatric or physical condition
Pregnancy	
Protocol Deviation	Repeat non-adherence of participant with protocol requirements or treatment
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pursue Alternative Treatment COVID-19 Pandemic Other
Death	

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.7.5).

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the

assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status of the participant is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL within 56 days.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as date of birth (month and year), sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical history

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

Any condition meeting the criteria of a SAE that occurs after signing the ICF but before the first dose of study intervention should be reported as described in Section 8.4.

8.2. Efficacy assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. HIV-1 RNA Sampling

Plasma for quantitative HIV-1 RNA will be generated at timepoints listed in the SoA (Section 1.3).

An HIV-1 RNA PCR assay with a LLOD of 40 copies/mL or lower will be used.

Details concerning the handling, labeling, and shipping of these samples will be provided in the laboratory manual.

In order to maintain the blind, HIV-1 RNA results will not be provided to site staff.

8.2.2. Lymphocyte Subsets by Flow Cytometry

Blood samples will be obtained from each participant for the analysis of lymphocyte subsets 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 provided in the laboratory manual.

8.2.3. 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 10.9).

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3)**.**

8.3.1. Physical examination

- A complete physical examination will include, at a minimum, assessments of the CV, respiratory, gastrointestinal, and neurological systems. A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Height and weight will also be measured and recorded. Height will be captured at Screening only. Weight will be captured at each visit to accurately calculate BMI and eGFR. For guidance on weight measurement see Section 8.3.1.1.

8.3.1.1. 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 (e.g., If measured at 10 am at initial measurement, attempt to have the participant measured at 10 am 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.

8.3.2. Vital signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).

Blood pressure and pulse measurements will be assessed in semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones). 3 consecutive blood pressure and pulse readings will be recorded at intervals of at least 1 minute. The first reading should be rejected. The average of the second and third readings should be recorded.

8.3.3. Electrocardiograms

See Table 7 and Table 8 in Section 8.5.

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 7.1.2 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

At each timepoint 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.

8.3.4. Clinical safety laboratory tests

See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with 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 or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- In the absence of a diagnosis, abnormal laboratory findings, assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).
- If clinically significant 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.
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g, SAE or AE or dose modification), then the results must be recorded.

Refer to the laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

- All study-required laboratory assessments will be performed by a central laboratory, with the exception of Screening laboratory assessments which may be performed at the local laboratory in exceptional circumstances, if this more readily facilitates evaluation of the eligibility of candidate study participants. The Investigator will review the local laboratory reports, confirm eligibility and document this in the eCRF (see Section 10.2). At the Screening site visit, the scheduled laboratory assessments should also be collected for analysis by the central laboratory. NOTE: For eligible participants on Study Day 1, all laboratory assessments should be repeated and performed by the central laboratory as described in the SoA (See Section 1.3).
- From Day 1 onwards, local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is

required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a treatment or a response evaluation or are considered clinically significant by the investigator (e.g., SAE or AE) the results must be entered in the eCRF.

8.3.5. Pregnancy testing

Participants who were female at birth are only eligible to participate if they are confirmed to be a PONCBP as defined in Section 10.4.

8.3.6. Suicidal ideation and behavior risk monitoring

VH3739937 is not a central nervous system active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation at supratherapeutic doses identified in one study with another MI, GSK3532795, all participants will undergo assessment for suicidality in this study. Any clinically diagnosed case of suicidality (using the C-SSRS as tool during Screening, on-treatment, and in follow-up) will result in exclusion from the trial or (if already randomized) immediate discontinuation from the study. Moreover, in these cases, the Investigator will arrange for urgent psychiatric evaluation and management.

Participants with HIV infection occasionally may present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with other ARTs such as INSTIs, including DTG. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants being treated with VH3739937 should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

When informed consent has been given, families and caregivers of participants being treated with VH3739937 should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.

Baseline assessment of SIB and intervention-emergent suicidal ideation and behavior will be monitored during this study using the C-SSRS. The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form

[Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Day 1 (Baseline) 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. The C-SSRS is to be administered by a clinician at the timepoints specified in the SoA (Section 1.3). The C-SSRS will be conducted electronically by computer/tablet connected to the internet.

Additionally, the investigator will collect information using the 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 behavior, a suicide attempt, or a completed suicide. The investigator will exercise their medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to GSK/ViiV Healthcare within 1 week of the investigator diagnosing a possible suicidality-related AE.

As described in Section 7.1.3, new onset suicidal ideation of concern to the Investigator (see below) at any time will result in immediate discontinuation from the study and the Investigator will arrange for urgent specialist psychiatric evaluation and management.

Emergent non-suicidal Psychiatric AE Evaluation and Management:

- 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 Investigator. Any pharmacotherapy should be discussed with the Medical Monitor.
- Any Grade 3 or 4 Psychiatric AE: As described in Section 7.1.3, a Grade 3 or 4 Psychiatric AE will result in discontinuation from the study and emergency psychiatric evaluation (including potential hospitalization and pharmacotherapy as indicated). A urine sample should be submitted for the Drugs of Abuse panel.

8.3.7. Study stopping rules and safety monitoring

Participant safety will be continuously monitored by the Medical Monitor and designated Safety Lead (or delegate) throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.

Once all participants in Part 1 (n=20) have completed Clinic Visit 6 (Study Day 8), all available preliminary unvalidated in-stream clinical data will be reviewed by the iDRC, for agreement on Part 2 (if opened) number of Cohorts (up to 3) and doses to be assessed.

Enrollment will be paused during the review. If data from Part 1 is considered sufficient to meet the objectives and endpoints of the study, no further enrollment into the study will take place (See Section 9.4).

8.3.8. GI Intolerability Evaluation and Monitoring Plan (with Stopping Criteria)

This section provides general guidance to the Investigator on the evaluation and management of primarily upper gastrointestinal symptoms (Table 5). 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 5 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, 2022].
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. [Mearin, 2016; Stanghellini, 2016]
PHYSICAL EXAMINATION	Physical examination should complement elements obtained from the history [Hasler, 2022]. 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.
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, 2008]. A major goal of therapy is directed at correcting the underlying identifiable medical or surgical abnormalities (e.g., perforation or infarction) [James, 2009; 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. PCR for viruses (e.g., CMV)

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 (e.g., 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 • 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 7.1.3).

8.4. Adverse Events (AEs) serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3

The investigator and any qualified designees are responsible for detecting, documenting, and recording 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 study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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.

8.4.1. Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SoA.

All AEs will be collected from the start of study intervention until the final follow-up visit at the timepoints specified in the SoA.

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 h, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. 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 resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.7.5.

8.4.4. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.

For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.7.6

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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

Female participants are only eligible to participate in the study if they are confirmed PONCBP as defined in Section 10.4).

In the unlikely event that a female participant does become pregnant, instructions for pregnancy follow-up are given below.

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

Details of all pregnancies in female participants will be collected after the start of study intervention and until 28 days after the final dose.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 h of learning of the female participant's pregnancy.

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 the sponsor within 24 h of the investigator becoming aware of it.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

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

8.4.6. Cardiovascular and death events

For any CV events detailed in Section 10.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

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

The Death eCRF 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.

8.4.7. Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The DREs listed in the CDC Classification System for HIV-1 Infections (Section 10.9) are common in participants living with HIV-1 and can be serious/life threatening:

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the HIV-associated conditions eCRF page if they occur, according to the timeframe defined in the CRF completion guidelines. These DREs will be monitored by a SRT on a routine basis.

NOTE: However, if any of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

OR

Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

OR

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.

8.4.8. Contact information for reporting SAEs

Table 6 Contact information for reporting SAEs

Contact for questions regarding SAEs, pregnancies or any other safety event that may meet a safety stopping criteria Contact the ViiV Healthcare medical monitor
Contacts for reporting SAEs, AESIs and pregnancies Available 24/24 h and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com

8.4.9. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

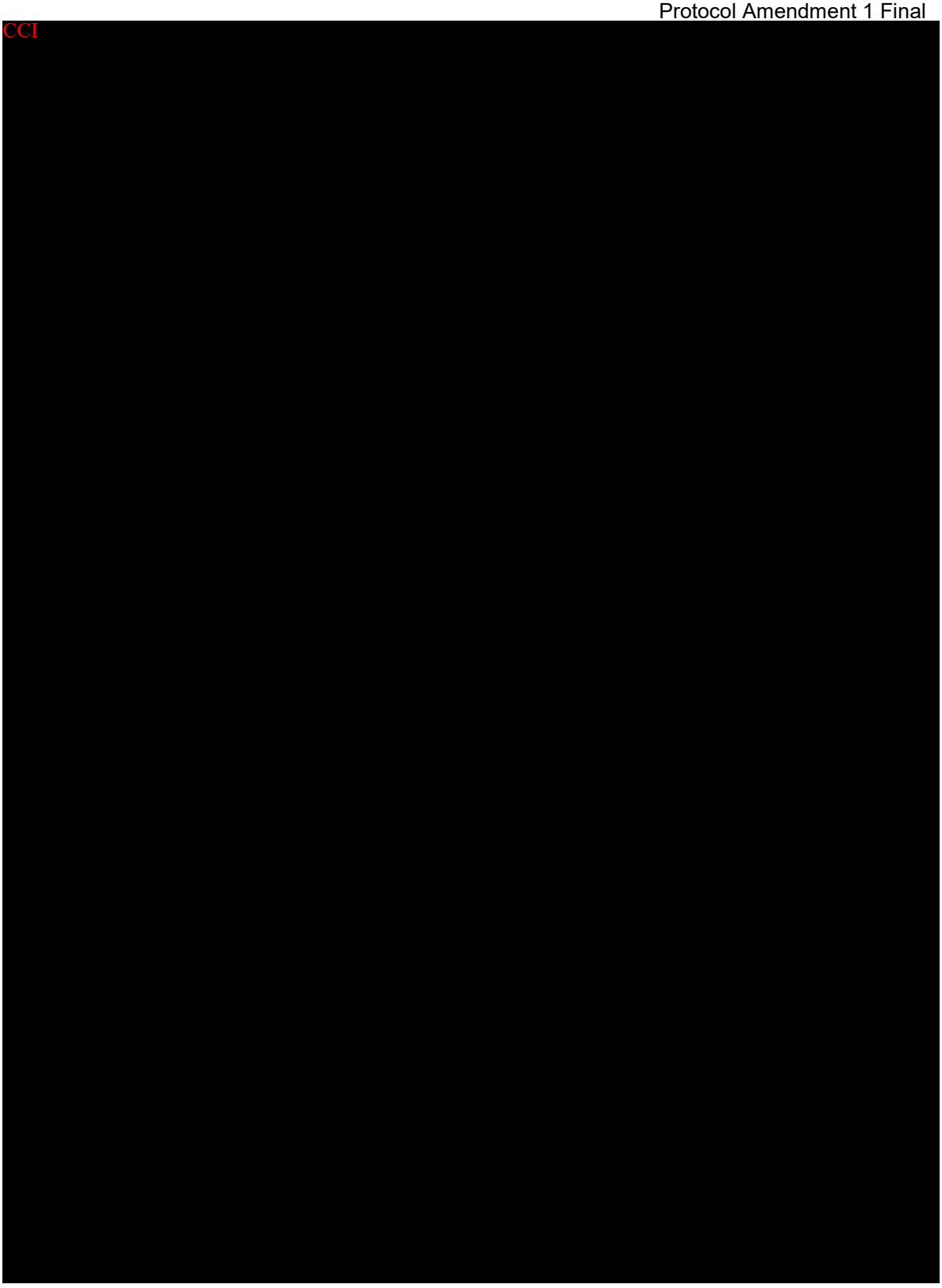
8.5. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of blood concentrations of VH3739937 at the visits specified in the SoA (Section 1.3) and as detailed in Table 7.
- A maximum of 10 samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the 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 the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of VH3739937. Each blood sample will be processed and divided into 2 aliquots (1 each for PK and a backup). Samples collected for analyses of VH3739937 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded, without first being anonymized.

- Once the plasma has been analyzed for VH3739937, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.
- Intensive PK sampling (Day 1 and Day 7 CCI) begins with a pre-dose sample in the morning on the day of the visit. On Day 7, the pre-dose sample should be taken approximately 24 h after the dose of study intervention from the previous day (Day 6).
- CCI
- It is critical to capture the exact date and time of each PK sample collection, even if drawn slightly off-schedule. If a sample collection time point is missed/late/not done within the specified window and the next collection time point has not yet been reached, collect the missed time point, and record the exact time of that collection, then get back on track for the next time point/on-time collection.
- Table 7 below lists the sampling schedule to be followed for the assessment of intensive PK CCI
- CCI
- Further details of PK blood collection and sample processing will be provided in the central laboratory manual.

CCI

CCI



CCI

[redacted]

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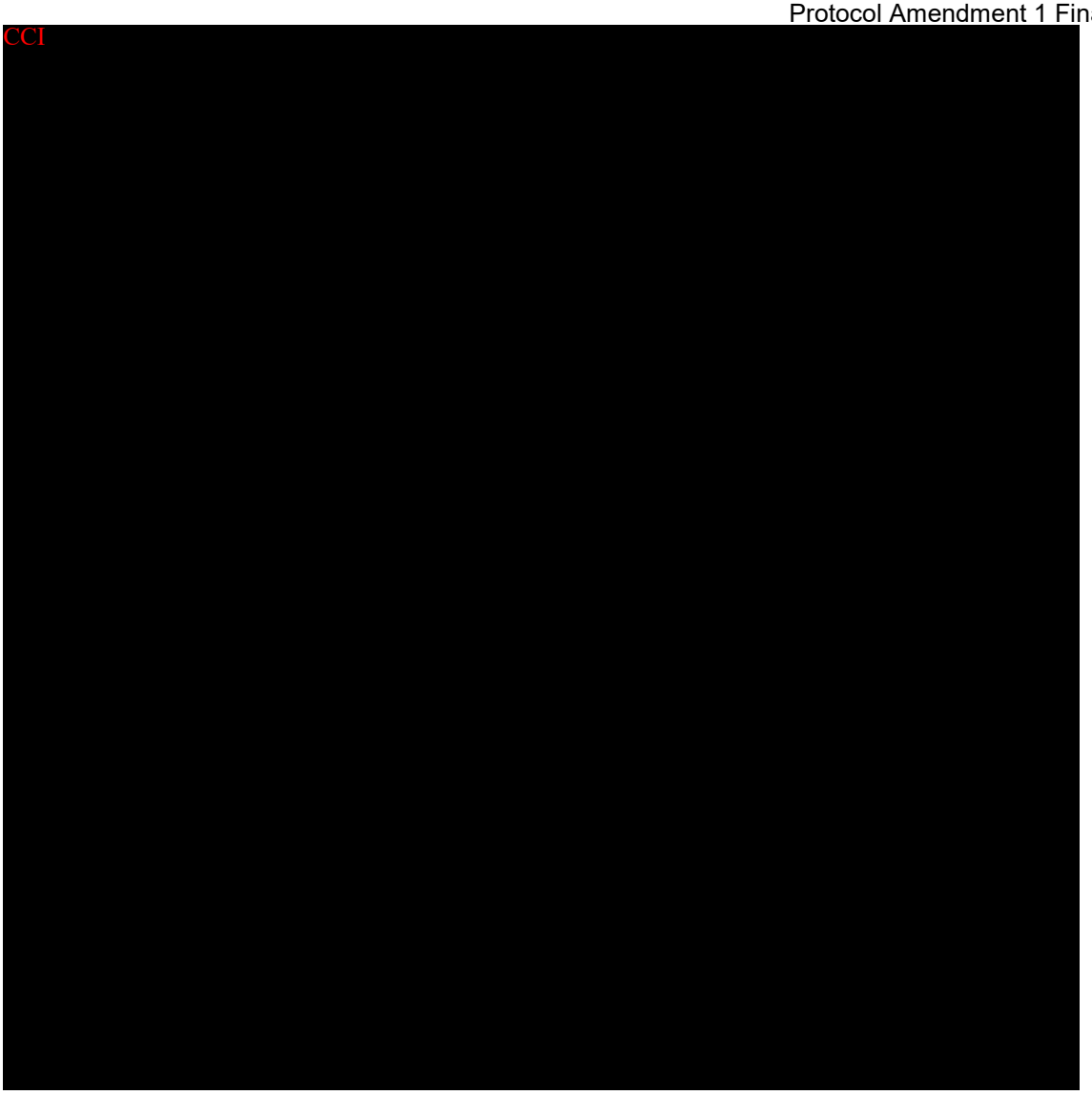

8.6. Pharmacodynamics

See Section 9.3.3.

8.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the 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 laboratory manual.

8.8. Biomarkers

8.8.1. Viral Genotyping and Phenotyping

Whole venous blood samples will be collected from each participant to provide plasma for viral genotype and phenotype analysis. Samples will be collected according to the schedule described in the SoA (Section 1.3) and as detailed in the laboratory manual.

Whole venous blood samples will be collected from each participant to provide "plasma for storage samples" according to the schedule described in the SoA (Section 1.3; for potential additional viral genotypic and phenotypic analyses) and as detailed in the laboratory manual.

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences.

The genotypic and phenotypic analyses will be performed by using Gag/PR assays, in which PCR amplification is used to generate HIV PCR amplicons including the Gag and the PR regions. Phenotypic analyses of the Gag/PR region will include susceptibility to VH3739937. Analysis will be done on samples collected on study Day 1 and Day 8 initially with other timepoints analyzed if indicated as data emerge for viral load response.

The results of any genotypic and phenotypic analyses are for research purposes only and will not be shared with investigators.

GSK/ViiV Healthcare may store samples for up to 15 years after the end of the study to achieve study objectives or other period as per local requirements. Additionally, with participants consent, samples may be used for further research by GSK/ ViiV Healthcare or others such as universities or other companies to contribute to the understanding of HIV-1 Infections or related conditions, the development of related or new treatments or research methods. For further detail, please see Section 10.5.

8.8.2. HIV-1 Exploratory Analysis

Additional exploratory analyses for HIV-1 treatment emergent changes during the course of monotherapy may include viral genotyping and/or phenotyping on a representative subset of Baseline samples or virologic analysis on stored plasma samples from other time points.

8.9. Immunogenicity assessments

Not applicable

8.10. Health economics or 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 primary objective of this study is outlined in Section 3 and will be addressed using an estimation approach (descriptive statistics) with no hypothesis testing. The primary treatment effect to be estimated is the maximum change from Baseline in plasma HIV-1 RNA over 7 days of VH3739937 treatment.

9.2. Analysis sets

Analysis Set	Definition	Analyses Evaluated
Screened	• All participants who are screened for eligibility	• Study Population
Randomized	• All participants who are randomly assigned to study treatment (i.e., VH3739937 or placebo) in the study	• Study Population
Safety	• All randomized participants who take at least 1 partial or full dose of study treatment • Participants will be analysed according to the treatment they actually received	• Safety
Full Analysis Set (FAS)	• All randomized participants who received at least one full dose of study treatment • Data will be reported according to the randomized study intervention	• Efficacy
Per-Protocol (PP)	• All participants in the full analysis set for whom there were no major protocol deviations that impact the primary analyses • Data will be reported according to the treatment actually received • Specific details of major protocol deviations that would exclude participants	• Efficacy

Analysis Set	Definition	Analyses Evaluated
	from the PP analysis set are provided in Section 9.3.1.1	
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 PK assessment (NQ values will be considered as non-missing values) • Data will be reported according to the actual study treatment	• PK

Analysis populations may be added, removed, or modified. Full details will be available in the final SAP.

9.3. Statistical analyses

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

9.3.1. General considerations

Data will be summarized by dose for VH3739937 and placebo, unless otherwise specified.

Data will be summarized either by visit or for the study intervention period and overall (i.e., study intervention period plus cART period) separately, as appropriate for each endpoint.

For all endpoints, except for ECG, the baseline value will be the latest pre-dose

assessment with a non-missing value, including those from unscheduled visits. Day 1 pre-dose ECGs will be performed in triplicate and the average of pre-dose triplicate measurements will be used as baseline.

Continuous and categorical variables will be summarized using the following descriptive

statistics, unless otherwise specified:

- Continuous data: n (number of participants used for the summary), arithmetic mean, SD, median, interquartile range, minimum and maximum. For PK data, geometric mean, SD of log-transformed data and geometric $\%CV_b$ may also be used.
- Categorical data: number and percentage of participants

9.3.1.1. Protocol Deviations leading to exclusion from PP analysis set

The SAP will describe the important protocol deviations leading to exclusion from the Per Protocol analysis set.

9.3.2. Primary endpoint/estimand analysis

Plasma HIV-1 RNA values will be used for the primary efficacy analysis. Change from Baseline will be calculated for each participant at each assessment time point during the study intervention period in the original and log10 scales. Maximum change from baseline during the study intervention period will be calculated for each participant from the set of available change from Baseline values at each assessment time point in the original and log10 scales. The log10 transformation is used to allow for direct comparisons with data from other compounds publicly available in the same scale, and hence aid in interpretation.

9.3.2.1. Definition of endpoint(s)/estimands

See Section 3 for definition of primary endpoint and estimand.

9.3.2.2. Main Analytical Approach

The primary efficacy analysis will be based on the FAS.

Maximum change from baseline in plasma HIV-1 RNA during study intervention period will be summarized by treatment (i.e., VH3739937) and dose level, and collectively for placebo, in original and log10 scales.

In addition, change from Baseline in plasma HIV-1 RNA at each assessment time point during study intervention period will be summarized by treatment, i.e., VH3739937 dose level, and collectively for placebo, in original and log10 scales.

Descriptive statistics will be provided as described in Section 9.3.1.

Handling of missing data and Intercurrent Events leading to exclusion of data

Any missing HIV-1 RNA data (e.g., due to missed visits in the clinic, lost to follow-up or for any other reason) will not be imputed and will remain missing. Whatever HIV-1 RNA data are available for a participant during study intervention and prior to starting cART will be used to calculate maximum plasma HIV-1 RNA.

Participants who withdraw from study prior to the end of study intervention period, preventing assessment of primary endpoint, no imputation will be performed for missed assessments after their study withdrawal.

9.3.2.3. Supplementary/supportive analysis/analyses

A supplementary analysis will be conducted to summarize maximum change from Baseline and change from Baseline by visit in plasma HIV-1 RNA based on the PP Analysis set.

Additional analyses may be conducted, including borrowing historical or contemporary placebo control data. Details of any of these analyses will be included in PDAP.

9.3.3. Secondary endpoint analyses

See Section 3 for definition of secondary endpoints and estimands.

9.3.3.1. Safety Analysis

All safety analyses will be performed on Safety Analysis set. Safety data will be presented in tabular format and summarized descriptively according to GSK's IDSL. No formal statistical analysis of the safety data will be conducted.

9.3.3.1.1. Analysis Method

The number and proportion of participants with AEs will be tabulated overall and by severity grade, by treatment and dose level. The number and proportion of participants with AEs leading to discontinuation of VH3739937 or placebo will also be tabulated. In AE tabulations, each participant's AE will be counted once under the maximum severity. AEs will be tabulated using latest version of MedDRA preferred terms. AEs will be tabulated for the study intervention period and overall (i.e., study intervention period plus SOC period) separately.

For liver panel laboratory parameters, summary statistics (e.g., mean, median, std etc.) of change from Baseline values by visit will be presented by treatment and dose level. Number and percentage of participants with maximum toxicity grade increase from Baseline for liver panel parameters will be presented by treatment and dose level; this will be done separately for the study intervention period and overall (i.e., study intervention period plus SOC period).

Handling of missing data and Intercurrent Events leading to exclusion of data

All available safety data will be considered in summaries of AEs and liver panel laboratory parameters within the respective period (e.g., study intervention or intervention plus SOC) regardless of whether study treatment was discontinued.

No imputation will be performed for missed assessments while participants are on study or after study withdrawal.

9.3.3.2. Pharmacokinetic Analyses

All pharmacokinetic analyses will be performed on the Pharmacokinetic analysis set.

9.3.3.2.1. Analysis Method

Plasma VH3739937 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 8.1 or higher, Phoenix (Pharsight Corporation) or comparable software to derive the PK parameters. This analysis will be based on actual sampling times recorded during the study. The various PK parameters will be inferred as data permits. Individual plasma PK parameters for each participant will be determined, including but not limited to Cmax and tmax.

Plasma concentrations will be presented in graphical form and will be summarized descriptively by treatment (i.e., VH3739937) and dose level. PK parameters will be summarized descriptively by treatment (i.e., VH3739937) and dose level. Descriptive summaries will be used as described in Section 9.3.1.

The data from this study may be combined with the data from other studies for a population PK analysis, which may be reported separately.

Handling of missing data and Intercurrent Events leading to exclusion of data

VH3739937 plasma concentrations and PK parameters derived after discontinuation of VH3739937 will be excluded from descriptive summaries.

More information on the handling of PK concentrations after partial/missed VH3739937 doses when summarizing trough (pre-dose) concentrations by visit will be provided in the SAP.

No imputation will be performed for missed plasma concentrations and PK parameters while on study or after study withdrawal.

9.3.4. Exploratory endpoint(s) analysis

Details on the analyses of exploratory endpoints and other analyses will be included in the SAP.

9.4. Interim analyses

An informal interim analysis will be conducted using available preliminary unvalidated in-stream unblinded clinical data once all participants (to include a minimum of 5 participants per active arm and 2 placebo participant) from Part 1 have, at a minimum, completed their Day 8 visit. GSK/ViiV Healthcare CPMS (and associates) may be provided individual participant level plasma drug concentration and viral load information at one or more time points prior to all participants in Part 1 having completed their Day 8 visit, to refine the population PK model and develop a PK/PD model that will be used to explore the exposure-response relationship between PK and viral load to determine whether additional doses need to be evaluated in optional Part 2 of the study.

The interim analyses will evaluate the PK and PD (antiviral activity) of each respective VH3739937 dose and inform if additional optional dosing arm(s) for VH3739937 will be evaluated in Part 2. Depending on the Part 1 results, a higher dose, lower dose, or a dose between the 2 QD doses evaluated in Part 1 may be evaluated in Part 2, CCI [redacted]. It is also possible that Part 2 will not be conducted if the doses evaluated in Part 1 adequately describe the exposure response of VH3739937. The interim results will also inform future clinical development of VH3739937.

The interim results are not intended for public dissemination. Criteria for data quality for data used in the interim analyses will be described in the study data management plan. Throughout the conduct of the study ViiV Healthcare/GSK (and associates) will be

blinded to the assignment for individual participants except for key roles necessary to prepare for and conduct the interim analyses. These roles will minimally include the clinical lead physician/medical monitor, safety physician/scientist, team lead, statistician, programmer, clinical pharmacologist(s), modeller(s) and clinical virologist who will have access to unblinded data. Moreover, unblinded data may be shared with GSK/ViiV Healthcare Medical Governance Committees (at their request and consistent with internal SOPs).

After the interim analysis, a final EoS analysis will be conducted after the completion of the study (i.e., when all participants complete the Day 25 visit, discontinue or are withdrawn) and final datasets authorization. At the EoS analysis all primary, secondary and exploratory endpoints will be evaluated with the exception of viral resistance and any exposure-responses analyses, which will be evaluated at a later stage and reported separately.

Additional interim analyses may be performed during the course of the study to inform internal decision-making activities. No changes to the conduct of the study will be implemented as a result of these analyses.

9.5. Sample size determination

The sample size is based on feasibility and no formal calculation of power or sample size has been performed.

9.5.1. Sample Size Considerations

Based on data from the short-term monotherapy study of the BMS-955176/GSK3532795 proof of concept study (AI468002), the GSK2838232 proof of concept study, and the GSK3640254 proof of concept study (208132), the distribution of maximum change from baseline VLD values on the log scale can be assumed to be normal.

Assuming normality, the sample size of N=6 participants per intervention cohort allows estimation of the mean maximum VLD in log10 scale with precision shown on Table 9 shows the expected precision of the estimated mean maximum VLD in log10 scale measured by the 95% CI width for various observed data variability assumptions as reflected by the sample SD.

Table 9 Expected precision (measured by the 95% CI width) of the estimated mean of maximum VLD in log10 scale for various assumptions of observed data variability for N = 6 participants

Sample SD	Precision (95% CI Upper Limit)
0.40	0.84
0.50	1.05
0.65	1.36
0.80	1.68

9.5.2. Sample Size Sensitivity

To evaluate study's sensitivity to sample size we calculated the expected precision of the estimated mean of maximum VLD in log10 scale for a treatment intervention for various sample sizes. Figure 3 shows the expected precision, measured by the 95% CI width, of the estimated mean maximum VLD in log10 scale for various sample sizes for a treatment intervention and various assumptions on the observed data variability (reflected by the sample SD).

Figure 3 Expected precision (measured by the 95% CI width) of the estimated mean of maximum VLD in log10 scale for various assumptions on observed data variability and sample size

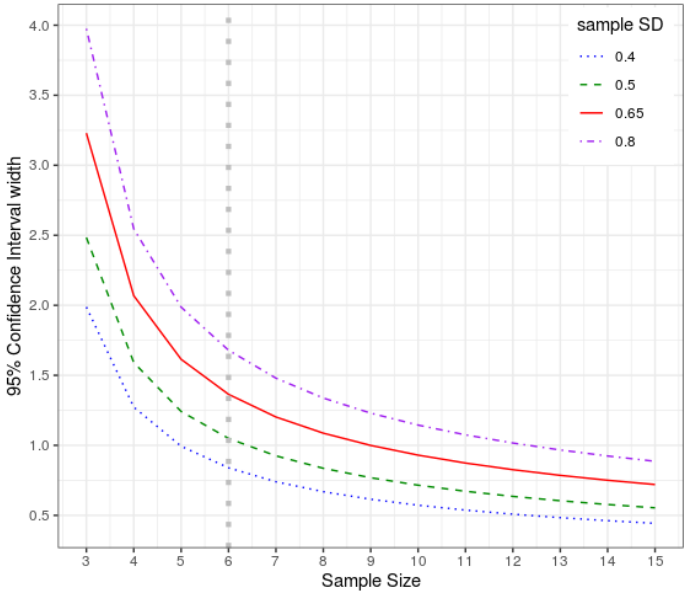

Figure 3 shows how the expected precision of the estimated mean of the maximum log10 VLD changes with an increase in the sample size for various observed data variabilities (measured by the sample standard deviation) within an active arm. Figure 3 indicates a smaller gain in the expected precision for increases of sample size beyond N=6 relative to gain in the expected precision up to N=6. For example, for observed data variability SD=0.65, increasing the sample size from N=4 participants to N=6 the precision of the estimated mean increases by 34%, whereas increasing the sample size from N=6 to N=8 the precision increases only by 20%. Of note, a much higher sample size is needed to achieve significant gains in precision, especially for smaller observed data variability. For example, for observed data variability SD=0.65, to get a ~40% more precise estimate of the mean maximum VLD a sample size of N=12 participants is needed. So, a sample size of N=6 participants per intervention cohort was considered appropriate for the study.

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH 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.
- Substantial amendments to the protocol (or non-substantial amendments where local regulations require) will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.
- ViiV Healthcare / GSK (alone or working with others) may use participants' coded study data and samples and other information to carry out this study; understand the results of this study; learn more about VH3739937 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have VH3739937 approved for medical use or approved for payment coverage.
- The ICF will contain a separate section that addresses the use of participant data and remaining samples for optional further research either related to the study or for other research not related to the study/disease. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate 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 related to the study and for further research not related to the study/disease. Participants who decline further research related to the study and/or not related to the study/disease will tick the corresponding "No" boxes.
- In case of unexpected pregnancy, participant must be informed that PII such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant.

10.1.4. Recruitment strategy

Approximately 50 participants will be screened globally, with the expectation of approximately 20 being enrolled into Part 1 of the study. Should Part 2 be required, approximately a further 50 participants will be screened, with the expectation of approximately 20 being enrolled. To recruit these participants, historical and current data

has been evaluated to determine the most suitable countries and sites to recruit the study population. Considerations have also been given to diversity targets and local availability of SOC treatment for participants from Day 8 onwards.

Recruitment will be monitored by GSK/ViiV Healthcare LOCs using real time monitoring of screening and enrolment information.

Recruitment will primarily be performed by the Investigators from their existing patient population.

If a study site considers it may be beneficial, IRB/IEC approved advertisements may be placed in public areas of the study site i.e., waiting rooms in order to increase awareness of the study.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. 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.
- GSK/ViiV Healthcare will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their 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, that their data will be used as described in the informed consent.
- The participant must be informed that their 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK/ViiV Healthcare and/or trusted third parties working on behalf of GSK/ViiV Healthcare and/or institutions working with GSK/ViiV Healthcare for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Committees structure

A SRT is in place for each GSK/ViiV Healthcare product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The

SRT contribute to the continual assessment of incoming new efficacy and safety information.

- All safety data collected will be summarized and reviewed by GSK/ViiV Healthcare SRT for agreement of next steps.
- The SRT is an internal ViiV Healthcare/GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety.
- In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to pause/stop the study.
    - Any deaths, regardless of causality
    - Adverse events and laboratory abnormalities as cited in Section 7.3 'Discontinuation of Study Intervention'
- Case unblinding may be performed for above reviews if this is considered necessary.

In addition, data from Part 1 will be reviewed by the Sponsor's internal safety review or other committee in order to determine whether initiation of enrollment into Part 2 of the study is required to address the primary objective of the study. Data will be reviewed once all participants in Part 1 have completed Day 8/Clinic Visit 6 and will include all available safety and virology data, together with PK data up to Day 8.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or ViiV Healthcare Clinical Study Register in compliance with applicable regulations/ViiV Healthcare policy. ViiV Healthcare will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, ViiV Healthcare will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. ViiV Healthcare will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- ViiV Healthcare will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

- ViiV Healthcare intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL plan or equivalent document to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- 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, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan or equivalent document.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different 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.

10.1.9. 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 eCRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site Termination

GSK/ViiV Healthcare 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 GSK/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 (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily 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 temporary 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.

10.1.11. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 10 Protocol-required safety laboratory tests

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry[e]			
BUN	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Albumin
Glucose[a]	Cystatin C	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	eGFR[b]
Calcium	GGT	Protein	Lipid profile[a] (Total cholesterol, HDL, LDL, Triglycerides)

Routine Urinalysis			
Specific Gravity	pH	Glucose	Protein
Blood	Ketones	Bilirubin	Urobilinogen
Nitrite	Leukocyte esterase by dipstick		
Microscopic examination if blood or protein is abnormal			
Other Tests			
Plasma HIV-1 RNA			
CD4+ and CD8+ cell count			
Serology: HIV antibody, HbsAg, anti-HBc, anti-HBs and HBV DNA (by PCR) if indicated, and hepatitis C antibody, with reflex to HCV RNA (by PCR) if positive (Screening)[d]			
Syphilis RPR			
Urine drug screen (to include at a minimum amphetamines, barbiturates, cocaine, opiates, marijuana, heroin, cannabinoids and benzodiazepines, buprenorphine, fentanyl, methadone)			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			

a) Glucose and lipid profile can be non-fasting except on Days 1, 8 and 25, as indicated in Section 1.3.
b) Glomerular filtration rate (eGFR) will be estimated by the central laboratory using the refitted, race-neutral Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIcr_R) method [Delgado, 2022]. In addition, GFR will be estimated by the central laboratory using the refitted, race-neutral CKD-EPI-cystatin C [Delgado, 2022] at Day 1 and when indicated by renal toxicity criteria.
c) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
d) HBV DNA will only be performed for participants with a positive anti-HBc and negative HbsAg and negative anti-HBs (past and/or current evidence).
e) Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6. In addition, the laboratory may perform Hepatitis E IgM and Cytomeglavirus IGM if required in the event of a liver event. All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK/ViiV Healthcare in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
f) Laboratory tests for eligibility may be performed by local laboratory in exceptional circumstances, however, central laboratory samples must also be collected at the screening visit. The results of each test used for eligibility must be entered in the eCRF.

The addresses of the clinical laboratories in charge of human biological sample testing are provided in a separate document ('List of clinical laboratories used for human biological sample analysis') and stored in TMF at the time of the protocol finalization.

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 Meeting 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 condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen). • "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 that 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, admission for routine examination.).
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. Pre-existing diseases will be recorded in the medical history section of the eCRF.
Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
DRE typically associated with the disease under study. These events will be recorded in the participant's eCRF and will be monitored by the SRT on a routine basis. However, if 1 or both of the following conditions apply, then the event should be reported promptly to GSK as an SAE (see Section 8.4.8):
The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
The investigator considers that there is a reasonable possibility that the event was related to the administration of the study intervention

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Other situations: Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or 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. Solicited events

Definition of solicited event
There are no solicited AEs in this study

10.3.4. Unsolicited AE

Definition of unsolicited AE
An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider).

Definition of unsolicited AE
The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Definition of CV events

CV definition:
Investigators will be required to fill out the specific CV event page of the eCRF 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

10.3.6. Definition of TEAE

TEAE Definition:
A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.7. Recording, assessment and follow-up of AE, SAE, and pregnancies

10.3.7.1. 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 reports, 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 the Sponsor in lieu of completion of the eCRF/required form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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 the Sponsor.

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.

10.3.7.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories according to the DAIDS toxicity scales (refer to Section 10.8).

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 one of the severity categories described in the functional DAIDS table shown in Section 10.8.

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.

Note: Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary.

10.3.7.3. Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

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.

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.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. 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 the Sponsor.

The investigator may change their 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.

10.3.7.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

Recovered/resolved

Recovering/resolving

Not recovered/not resolved

Recovered with sequelae/resolved with sequelae

Fatal (SAEs only).

10.3.7.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor 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 the Sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to the Sponsor within 24 h of receipt of the information.

After the initial AE/SAEpregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs (as defined in the Section 10.3.2), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until the last study visit or until the participant is lost to follow-up.

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last study visit.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper or electronic pregnancy follow-up report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.7.7.

10.3.7.6. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.7.7. Reporting of SAEs and pregnancies

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor 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 h.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any ViiV Healthcare/GSK non-IMP they will report these events to ViiV Healthcare/GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

- Contacts for SAE reporting can be found in Section 8.4.8.

SAE Reporting to the Sponsor **via Paper Data Collection Tool**

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- 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 timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Person of Nonchildbearing Potential (PONCBP)

Participants who were female at birth and are in the following categories are considered PONCBP:

- **Premenarchal: Tanner stage 1 (prepubertal)**

Permanently sterile due to one of the following procedures:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

For permanently sterile individuals 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. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- **Postmenopausal female**

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

Not applicable

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and 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 from consenting participants.
- DNA samples will be used for research related to VH3739937 or HIV-1 infection and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to VH3739937 or interventions of this drug class and HIV-1 infection. 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).
- Additional analyses of DNA samples may be conducted 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 VH3739937 or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR 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 VH3739937 or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver safety: suggested actions and follow-up assessments

Phase 2 Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology

Phase 2 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥3xULN

Bilirubin[1, 2]	ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN and INR>1.5

Required Actions, Monitoring and Follow-up Assessments

Actions	Follow-Up Assessments
• Immediately discontinue study intervention • Report the event to GSK **within 24 h** • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-Up Assessment column. • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) MONITORING: If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24 h • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5): • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24-72 h	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for PK analysis, obtained within 60 h after last dose[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH),), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications. • Record alcohol use on the liver event alcohol intake form. If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to

• Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline RESTART/RECHALLENGE • Do not restart/rechallenge participant with study intervention since not allowed per protocol; continue participant in the study for any protocol-specified follow-up assessments.	assess potential acetaminophen contribution to liver injury unless acetaminophen use very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialist if available: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for subject if ALT ≥3xULN and total 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 total bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. 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. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HbsAg and HBcAb ; hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to pk blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual

10.7. Appendix 7: Toxicity Management

Adverse events that occur during the study 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.

Study drug may be interrupted at the discretion of the investigator and according to the severity of the AE.

No toxicity-related dose reductions of study drugs will be allowed. Guidance is provided below on subject management and study drug interruptions based on the severity of the AE for specific toxicities. All changes in study drug must be accurately recorded in the participant's eCRF.

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 or toxicity that the investigator considers related to the study drugs should have study treatment permanently discontinued and be rechecked each week (at minimum) until the resolution of the AE .

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 drug if the investigator has compelling evidence that the toxicity is not related to study treatment.

Grade 4 Toxicity/Adverse Event

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.

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).

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 drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 7.1.1 and Section 10.6.

Hypertriglyceridemia/Hypercholesterolemia

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

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 subject has abstained from exercise for >24 h. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study drugs, study treatment should be discontinued and the subject withdrawn from the study

RASH

Grade 1 rash

Participants with an isolated Grade 1 rash may continue study drug 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 drug for an isolated Grade 2 rash. However, study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash with evidence of systemic involvement (e.g. concurrent fever, an increase in AST/ALT or eosinophilia). The participant should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops (which would indicate a Grade 3 rash, at minimum).

Grade 3 or 4 rash

Participants should permanently discontinue study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) for a related Grade 3 or any Grade 4 rash. 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).

10.8. Appendix 8: Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events 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 utilized for AE reporting. A grading (severity) scale is provided for each AE term. The investigator will make an assessment of intensity for each AE and SAE reported during the study. For more information, please refer to the DAIDS grading table Version 2.1, July 2017 at (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).

The Investigator may contact the ViiV Healthcare Medical Monitor with questions on estimating the severity grade for parameters not identified in the original table.

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
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	>40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81 cm^2)	Erythema OR Induration OR Edema >9 cm any diameter (or >81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤2.5 cm diameter	Erythema OR Induration OR Edema >2.5 cm diameter but <50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with <48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	**≥**180 mmHg systolic OR **≥**110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from >160-179 (systolic) and to ≥100 -109 from >100-109 (diastolic) and in Grade 3 to ≥180 from >180 (systolic) and to ≥110 from >110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval >0.25 sec	Type II 2nd degree AV block OR Ventricular pause >3.0 sec	Complete AV block
Pediatric ≤16 years	1st degree AV block (PR >normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc				
Adult >16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval <0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diarrhea				
Adult and Pediatric ≥1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (<24 h) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 h	Persistent nausea resulting in minimal oral intake for >48 h OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalizatio n indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Developmental delay – **Pediatric ≤16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric <18 years**	Seizure, generalized onset with or without secondary generalization, lasting <5 minutes with <24 h post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 h post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow <25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric <14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bone Mineral Loss				
Adult ≥21 years	BMD t-score -2.5 to -1.0	BMD t-score <-2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric <21 years	BMD z-score -2.5 to -1.0	BMD z-score <-2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption <25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption >75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption >75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

10.9. Appendix 9: CDC Classification for HIV 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.

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