CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	VH4524184
Other Study Intervention(s)	N/A
Study Identifier	218806
EU CT Number	2023-507173-18-00
Approval Date	29 Sep 2023
Title	A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH4524184 in HIV-1 Infected Treatment Naïve Adults
Compound Number/Name	GSK4524184 (also known as VH4524184)
Brief Title	VH4524184 Proof-of-Concept in Treatment-Naïve Adults Living with HIV-1
Sponsor	**ViiV Healthcare group of companies** **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, US
Sponsor signatory	Scott McCallister, MD Vice President and Head, Physician Center of Excellence

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

Protocol 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.
- 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 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 and the express physical and/or digital informed consent of the participant.
- 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 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 will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply ViiV Healthcare 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 may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide ViiV Healthcare 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)	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
%CVb	Percentage between-participant coefficient of variation
ADR	Adverse Drug Reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AIH	Autoimmune Hepatitis
ALT	Alanine aminotransferase
Anti-HBc	Antibody to Hepatitis B core antigen / Hepatitis B core antibody
Anti-HBs	Antibody to Hepatitis B surface antigen
ART	Anti-retroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC(0-∞)	Area under the curve zero to infinity
BLQ	Below the limit of quantification
BMI	Body Mass Index
BUN	Blood urea nitrogen
CA	Competent authority
CCI [redacted]	
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease - Improved Prediction Equations
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system

Abbreviation	Definition
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019 or Coronavirus
CPK	Creatine phosphokinase
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modeling and Simulation
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CSSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRE	Disease-related event
CCI [redacted]	
EC90	Concentration of drug required for 90% inhibition of the viral replication
ECG	Electrocardiogram
ED	Early discontinuation
EMA	European Medicines Agency
EOS	End-of-study
FAS	Full analysis set
FDA	Food and Drug Administration, United States of America
FSFV	First participant first visit

Abbreviation	Definition
FSH	Follicle stimulating hormone
FTiH	First-time in human
GCP	Good clinical practices
GGT	Gamma glutamyl transferase
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
H	Hour
HbcAb	Hepatitis B core antibody / Antibody to Hepatitis B core antigen
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B virus deoxyribonucleic acid
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCVAb	Hepatitic C virus antibody
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HIV-1 RNA	human immunodeficiency virus type 1 ribonucleic acid
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICSR	Individual case safety reports
IDSL	Integrated data standards library

Abbreviation	Definition
IEC	Independent ethics committee
Ig G	Immunoglobulin G
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
INR	International normalized ratio
CCI	[redacted]
IRB	Institutional review board
IUD	Intrauterine device
IWRS	Interactive web response system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LSLV	Last participant last visit
MAD	Multiple Ascending Dose
Max	Maximum
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDI	Metabolism dependent inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Min	Minute or minimum
MSDS	Material Safety Data Sheet
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse effect level

Abbreviation	Definition
NQ	Non-quantifiable
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PI	Personal information
PI	Principal Investigator
CCI	[redacted]
PK	Pharmacokinetic
POC	Proof of concept
POCBP	Participant of childbearing potential
PONCBP	Participant of nonchildbearing potential
POP PK	Population pharmacokinetics
PP	Per protocol
PrEP	Pre-exposure prophylaxis
PSRAE	Possible Suicidality-Related AE
PT	Prothrombin time
PTT	Partial thromboplastin time
PWH	Persons with HIV
QTc	Corrected QT interval
QTcF	QT Interval corrected for heart rate according to Fridericia's formula
QTL	Quality tolerance limit
RBCs	Red blood cells
RNA	Ribonucleic acid
RPR	Rapid plasma regain

Abbreviation	Definition
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SIB	Suicidal ideation and behavior
SoA	Schedule of activities
SoC	Standard of care
SoC ART	Standard of care antiretroviral therapy
SRT	Safety Review Team
SUSARs	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
tmax	Time to maximum observed plasma concentration
TN	Treatment-naïve
TOC	Table of contents
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VH	ViiV Healthcare
VLD	Viral load decline
VSLC	ViiV Healthcare's Safety and Labelling Committee
WBC	White blood cell

Abbreviation	Definition
WT	Wild type

Term	Definition
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.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Evaluable	Evaluable participants are defined as those who have PK concentration data to allow estimation of the maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 10
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, 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. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
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

Term	Definition
	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
Participant number	A unique identification number is 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
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	This term refers to the visit conducted in the place other than the study site.
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).
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).

Term	Definition
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH4524184 in HIV-1 Infected Treatment Naïve Adults

Brief Title: VH4524184 Proof-of-Concept in Treatment-Naïve Adults Living with HIV-1

Rationale:

VH4524184 is a CCI [redacted] The in vitro antiviral potency of VH4524184 is comparable CCI [redacted] with a likely high genetic barrier to resistance.

This proof of concept (POC) study is designed to gain information on the antiviral effect, safety, tolerability and pharmacokinetic (PK) properties of VH4524184 orally administered to adults infected with HIV-1 who have yet to initiate treatment.

Clinical development of VH4524184 is ongoing. Study 218803 is an ongoing first time in human (FTiH) study evaluating the safety, tolerability and PK properties of CCI [redacted] VH4524184 in healthy participants and 218804 is a planned FTiH study evaluating the safety, tolerability and PK properties of CCI [redacted] VH4524184 in healthy participants. Study 218803 has shown VH4524184 to be generally well-tolerated in healthy participants to date (63 participants received VH4524184 as of 27 July 2023) and has thus far demonstrated a favorable PK profile suitable for progression to treatment-naïve (TN) adults with HIV-1 in this Phase 2a POC 10-day, monotherapy study, CCI [redacted].

The data gathered from this study, together with data from the ongoing Phase 1 studies CCI [redacted], will inform subsequent clinical trials and Phase 2b clinical development.

Objectives, Endpoints, and Estimands:

Objective(s)	Endpoint(s)
Primary	
• To evaluate the antiviral activity of orally administered VH4524184 in TN participants with HIV-1 during 10 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 10.
Secondary	
• To assess the safety and tolerability of orally administered VH4524184	• Incidence of adverse events (AEs), severity of AEs and proportion of participants who discontinue treatment due to AEs • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameter (Alanine Transaminase (ALT), Aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase, albumin and total protein)
• To characterize the pharmacokinetic profile of orally administered VH4524184	As data permits, PK measures that include: • Maximum observed plasma drug concentration (Cmax), • Time to maximum observed plasma drug concentration (tmax), • Concentration on Day 10
• To evaluate any relationship between VH4524184 exposure and change in plasma HIV-1 RNA	• Correlation of VH4524184 PK parameters with maximum plasma HIV-1 RNA change from baseline through Day 10
• To assess the occurrence of emergent genotypic or phenotypic resistance after 10 days of monotherapy with VH4524184	• Genotypic and phenotypic data from baseline (Day 1) and Day 10 will be compared for amino acid substitutions and VH4524184 fold change IC50.
• To assess the immunologic effects of VH4524184 when administered over 10 days in participants living with HIV	• Change from baseline in CD4+ T-cell count to Day 10
Tertiary	
• To further assess the safety and tolerability of orally administered VH4524184	• Post baseline values and changes over time of vital signs, electrocardiogram (ECG) parameters and suicidality scores. • Absolute values, change from baseline and maximum toxicity grade increase from baseline for hematology, coagulation and remaining chemistry panels

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 VH4524184 over 10 days in up to approximately 28 antiretroviral therapy (ART) naive adults with HIV-1 and detectable viremia.

This study will be conducted in 2 parts. In Part 1, 21 treatment naïve (TN) participants will be randomized to 1 of 3 cohorts. Within each cohort, 6 participants will receive VH4524184 and 1 will receive matching placebo CCI [redacted]

Part 2 of the study is optional. The conduct of Part 2 is dependent on the informal interim evaluation of the exposure-antiviral response data from Part 1 using available preliminary clinical data from Part 1. Interim analysis of Part 1 will determine if evaluation of a fourth dose of VH4524184 would be informative to properly characterize the exposure-antiviral relationship. If evaluation of a fourth dose is needed, Part 2 will be conducted and will include 1 additional cohort in which up to 6 participants would receive VH4524184 and 1 would receive matching placebo. Part 2 may evaluate 1 additional dose, with the dose and frequency informed by PK/PD modelling of Part 1 data.

In both Part 1 and Part 2, each dose of VH4524184 will be evaluated as double-blind (Sponsor unblinded) monotherapy for 10 days (primary endpoint). On Day 10, participants will start open-label standard-of-care (SOC) antiretroviral therapy (ART) that is selected by the investigator and locally sourced. Participants will be followed weekly through Day 38. CCI [redacted]

All participants will be screened for eligibility preferably within approximately 7 to 14 days before being randomized into a 10-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.

Following screening, the study requires a total of 9 in-clinic visits (5 in-clinic visits will occur in the Monotherapy Period; 4 in-clinic visits will occur in the Open Label Follow-Up Period) and 3 virtual visits (3 virtual visits will occur in the Monotherapy Period; participant may choose to attend the visit in-clinic and this is acceptable). CCI [redacted]

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 1, 2 and 3, and optional cohort 4) 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.

Total duration of study participation is approximately 45 to 66 days based on the following:

- **Screening Period:** 7 to 14 days, with a maximum of 28 days permitted in some cases for screening/qualification period.
- **Monotherapy Period:** 10 days for treatment with the study intervention and assessment at all planned visits.

- **Open Label Follow-up Period:** 28 days for follow up visits while on SOC ART including the final follow up visit.

See Section 1.3 (Schedule of Activities) for additional details of activities during screening, the monotherapy period and the standard of care (SOC) period.

Number of Participants:

Approximately 28 antiretroviral therapy (ART) naïve participants may be enrolled in this study. Part 1 of the study will enroll approximately 21 participants. If Part 2 of the study is conducted, approximately 7 additional participants will be enrolled.

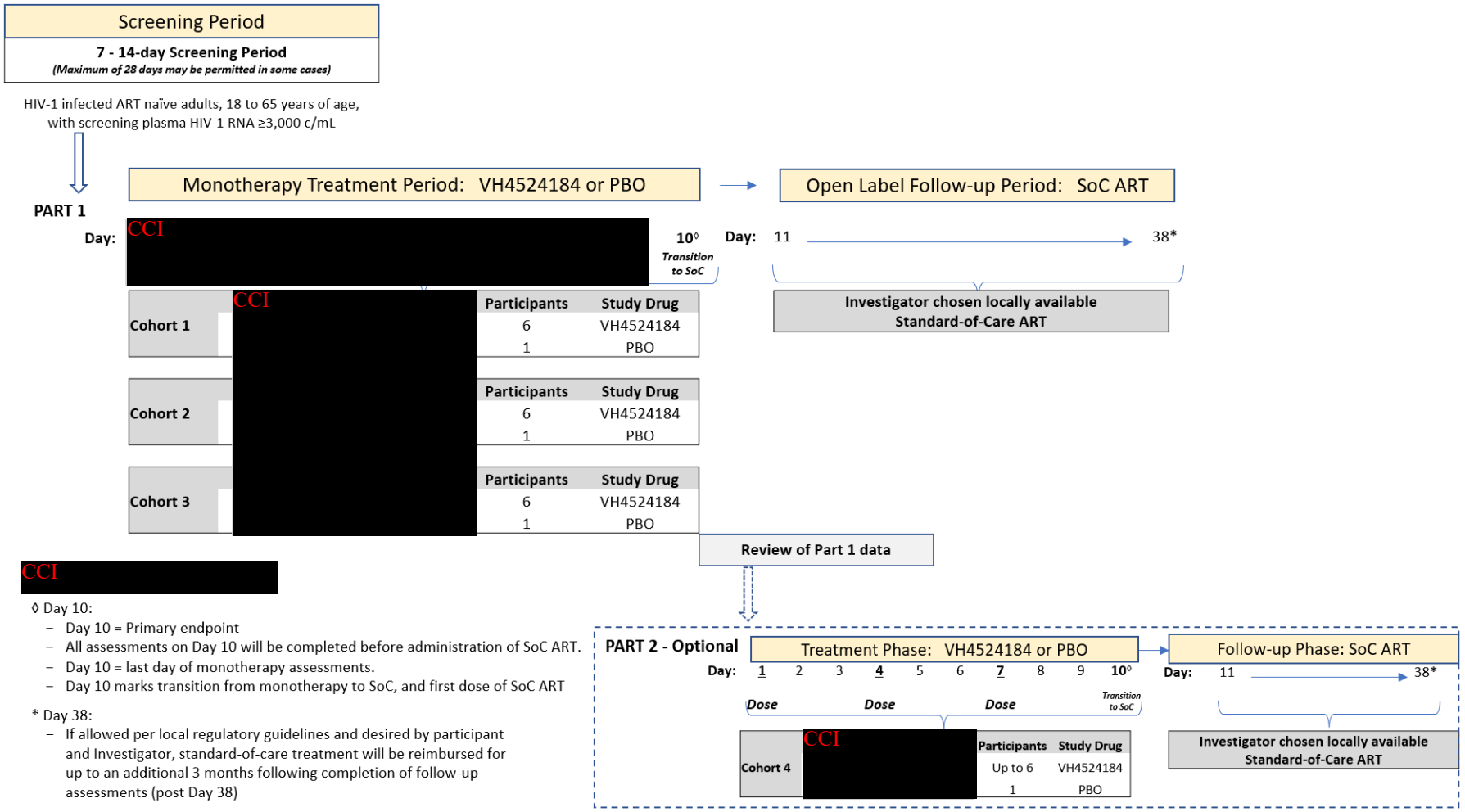
Data Monitoring/Other Committee:

A safety review team (SRT) is in place for each 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 blinded assessment of incoming new efficacy, safety and PK information. An external data and safety monitoring committee is not utilized in this study due to the relatively small size and early phase of the trial. This is further supported by the lack of significant safety findings from the available pre-clinical toxicity studies and preliminary clinical study of VH4524184.

ViiV Healthcare Safety and Labelling Committee (VSLC) is a governance group that will review data and the team's recommendation when any pausing/stopping rules are met. The VSLC will govern whether enrollment may be resumed/modified, a given treatment arm will be stopped, or the study stopped. The VSLC is comprised of senior representatives from various departments, including clinical development, safety, toxicology, pharmacovigilance, epidemiology, and medical affairs.

1.2. Schema

Figure 1 Study design overview



1.3. Schedule of activities (SoA)

The schedule of study visits and expected study procedures and activities are detailed in Table 1 (Screening Period, Monotherapy Period) and Table 2 (Open Label Follow-up Period and Early Discontinuation Visit).

While unlikely, the timing of assessments in Part 2 may be adjusted based on the interim analyses of the PK and/or antiviral results to ensure appropriate monitoring (e.g., to obtain data closer to the time of peak plasma concentrations or to maximal viral load decline). Any non-safety driven changes in the timing of the planned study assessments will be documented and communicated to investigators but will not constitute a protocol amendment.

Any emerging safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF will be approved by appropriate regulatory agencies and IECs/IRBs before implementation.

1.3.1. Screening and Monotherapy Period

Table 1 Screening and Monotherapy Period Schedule of Activities

Clinical Procedures	Screening	VH4524184 Monotherapy Treatment Period (Double Blind) Day 1→Day 10									
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6	Visit 7		Visit 8
	~7 to 14 days before Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
	Screening: In an effort to minimize delays to starting the open-label standard-of-care combination antiretroviral regimen, the screening period will be conducted in as short a time as possible and ideally within 14 days. However, if necessary, screening period may be extended up to 28 days to allow receipt of all screening results and/or to accommodate scheduling.										
Visits											
Outpatient visit	CCI [redacted]										D10
Telephone call (Clinic visit allowed)	.	.	.	*D3*		*D5 or D6*		.	*D8 or D9*		.

Notes

The Monotherapy Treatment Period requires a minimum of 8 visits over a 10-day period.

CCI [redacted]

- Days 1, 2, 3, 4, 7 and 10 are fixed visits. No window.
- Visit 5 may be conducted on Day 5 or 6.
- Visit 7 may be conducted on Day 8 or 9.
- Assessments at Visit 3 (Day 3), Visit 5 (Day 5 or Day 6), and Visit 7 (Day 8 or Day 9), may be conducted by telephone to minimize participant burden, although the participant may choose to attend the visit in the clinic, and this is acceptable.
- Day 10: Complete all Day 10 assessments prior to the start of standard of care ART.

The visit schedule for each participant will be pre-planned and weekend, work schedules, and clinic hours will be appropriately considered.

Order of assessments: Assessments, should occur in the following order:

1) ECG (if applicable); 2) Vital sign assessment; (3) eCSSRS; 4) Blood draw (on PK days, HIV RNA to be collected at same time as pre-dose PK sample [with no

Clinical Procedures	Screening	VH4524184 Monotherapy Treatment Period (Double Blind) Day 1→Day 10										
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6	Visit 7		Visit 8	
	~7 to 14 days before Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Notes
												preference as to which is drawn first]) CCI [redacted] All Day 10 assessments must be completed prior to administration of the first dose of standard of care ART.
Clinical and Other Assessments												
Informed consent	S	.	.	.	.	.	.	.	.	.	.	
Confirmation of no prior use of Anti-retroviral Therapy	S	D1	.	.	.	.	.	.	.	.	.	
Inclusion / Exclusion Criteria	S	D1	.	.	.	.	.	.	.	.	.	See Section 5.1 and Section 5.2
Demography	S	.	.	.	.	.	.	.	.	.	.	
Medical History	S	D1	.	.	.	.	.	.	.	.	.	Smoking history and alcohol intake to be included within the review of medical history. See Section 8.1.2
CDC HIV Classification	S	D1	.	.	.	.	.	.	.	.	.	See Section 10.7: Appendix 7.
12-lead ECG	S	D1	.	.	.	.	.	.	.	.	.	ECG obtained locally (site). QT interval corrected for heart rate according to Fridericia's formula (QTcF). • Screening: Collect single ECG reading to determine eligibility. A single repeat is allowed, if needed. CCI [redacted] See Section 7.1.3, Section 8.3.3.
Vital Signs	S	D1	D2	.	D4	.	.	D7	.	.	D10	Body temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests). See Section 8.3.2.
eCSSRS suicidality	S	.	.	.	.	.	.	.	.	.	D10	See Section 8.3.6.

Clinical Procedures	Screening	VH4524184 Monotherapy Treatment Period (Double Blind) Day 1→Day 10										
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6	Visit 7		Visit 8	
	~7 to 14 days before Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Notes
Physical exam	S (c)	D1 (b)	D2 (b)	.	.	.	.	.	.	.	D10 (b)	Complete (c) physical exam to be performed at Screening and Day 38 or at Early Discontinuation (ED) and will include assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Brief (b) physical exam to be performed at Day 1, Day 2, and Day 10, and may be targeted to include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). At the discretion of the investigator, a brief physical examination may be made a complete physical examination. Any abnormalities to be recorded as AEs. See Section 8.3.1
Height, Weight, BMI	S	.	.	.	.	.	.	.	.	.	D10	Height, and weight to be measured at screening to calculate BMI. Height from screening can be used to calculate BMI on Day 10, Day 38/ED.
AE/SAE assessment	S	D1	D2	D3	D4	D5 or D6		D7	D8 or D9		D10	• AE/SAE assessment, HIV-associated conditions, and concomitant medication reviews must be conducted with a participant during each day indicated. On the day when the participant does not come to the clinic, these assessments can be done via telephone. • Non-serious AEs are assessed from the time of first dose. • Serious AEs (SAEs) are assessed from the time of signing informed consent until the final visit in the Follow-up Phase.
HIV-associated conditions	S	D1	D2	D3	D4	D5 or D6		D7	D8 or D9		D10	
Concomitant medication review	S	D1	D2	D3	D4	D5 or D6		D7	D8 or D9		D10	

Laboratory Assessments												
Hepatitis B and C serologies	S	.	.	.	.	.	.	.	.	.	.	See Appendix 10.2 for details of clinical laboratory tests.
Syphilis RPR	S	.	.	.	.	.	.	.	.	.	.	
Drug, alcohol and cotinine screening	S	.	.	.	.	.	.	.	.	.	.	
Follicle stimulating hormone and estradiol	S	.	.	.	.	.	.	.	.	.	.	To be completed as needed in participants (female sex assigned at birth) of nonchildbearing potential (PONCBP) to confirm post-menopausal status.
Pregnancy Test	S (s)	D1 (u)	D2 (u)	.	D4 (u)	.	.	.	.	.	D10 (u)	To confirm that participants (female sex assigned at birth) of childbearing potential are not pregnant. (s)= serum; (u) urine. If urine test cannot be confirmed as negative, a serum test is required.
Plasma for HIV-1 genotype/phenotype	S	D1	D2	.	D4	.	.	D7	.	.	D10	
Lymphocyte T-cell subsets (CD4, CD8)	S	D1	.	.	.	.	.	.	.	.	D10	
Hematology / Chemistry / Coagulation/ Urine	S	D1	D2	.	D4	.	.	D7	.	.	D10	See Appendix 10.2 for details of clinical laboratory tests. Includes fasting glucose and fasting lipid panel.
Plasma for storage	S	D1	D2	.	D4	.	.	D7	.	.	D10	Plasma samples for storage will be collected at each outpatient visit, starting at Screening 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 may be utilized for additional research on antiretroviral resistance and/or HIV-1 disease biology/host immune response.
HIV-1 RNA	S	D1	D2	.	D4	.	.	D7	.	.	D10	CCI [redacted]

Plasma PK sampling	CCI [redacted]											
	Study Treatment											
Interactive Web Response System for Central Randomization	.	D1	.	.	.	.	.	.	.	.	.	
VH4524184/placebo administration	CCI [redacted]											
Dispensation of standard of care ART	.	.	.	.	.	.	.	.	.	.	D10	Standard of care antiretroviral therapy (SoC ART) will be chosen by the investigator. The first dose of SoC ART will be at Day 10, after the completion of all Day 10 assessments. Choice of SoC ART will be informed by local treatment guidelines, accepted clinical practice and accessibility. If allowed per local regulatory guidelines and desired by participant and Investigator, SoC treatment will be continued for up to an additional 3 months following completion of follow-up assessments (post Day 38)
Adherence counselling	.	.	.	.	.	.	.	.	.	.	D10	Adherence counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care

												and site SOPs. Counseling should be provided in a participant-centered manner, tailored as needed to the information, skills building, and support needs of each participant. Discussions to be documented within site source files.

AE= Adverse Events; (b)= Brief physical exam; BMI= Body Mass Index; (c)= Complete physical exam; CDC= Centers for Disease Control and Prevention; D1= Day 1; D2=Day 2; D3=Day 3; D4=Day 4; D5=Day5; D6=Day 6; D7= Day 7; D8=Day 8; D9= Day 9; ECG= electrocardiograph; HIV-1= human immunodeficiency virus type 1; (i)= Intensive PK visit; PK= Pharmacokinetic RNA= ribonucleic acid; SAE= Serious Adverse Events; S= Screening; Standard of Care antiretroviral therapy = SoC ART; VH4524184=Investigational Product

1.3.2. Open Label Follow-up Period

Table 2 Open Label Follow-up Period Schedule of Activities

Clinical Procedures	Open Label Follow-Up Period				Early Discontinuation	Notes
	Visit 9	Visit 10	Visit 11	Visit 12		
	Day 17 (+/- 2 day)	Day 24 (+/- 2 day)	Day 31 (+/- 2 day)	Day 38 (+/- 2 days)		
Visits						
Outpatient visit	D17	D24	D31	D38	ED	Early Discontinuation: Additional follow-up visits/contacts beyond Day 38 are permitted if a participant experiences a safety event that requires follow-up monitoring.
Clinical and Other Assessments						
12-lead ECG	.	.	.	D38	ED	12-lead ECG schedule: Day 38 or at Early Discontinuation- single reading.
Vital Signs	D17	D24	D31	D38	ED	
eCSSRS suicidality	.	.	.	D38	ED	
Physical exam	D17 (b)	D24 (b)	D31 (b)	D38 (c)	ED (c)	Complete (c) physical exam to be performed at Screening and Day 38 or at Early Discontinuation and will include assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Brief (b) physical exam to be performed at Day 17, Day 24 and Day 31, and may be targeted to include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). At the discretion of the investigator, a brief physical examination may be made a complete physical examination. See Section 8.3.1. Any abnormalities to be recorded as AEs.
Height, Weight, BMI	.	.	.	D38	ED	Height and weight to be measured at screening to calculate BMI. Height from screening can be used to calculate BMI on Day 10, Day 38/ED.
AE/SAE assessment	D17	D24	D31	D38	ED	• AE/SAE assessment, HIV-associated conditions, and concomitant medication review must be conducted with a participant during each day indicated. • Non-serious AEs are assessed from the time of first dose. • Serious AEs (SAEs) are assessed from the time of signing informed consent until the final visit in the Follow-up Phase.
HIV-associated conditions	D17	D24	D31	D38	ED	
Concomitant medication review	D17	D24	D31	D38	ED	

Clinical Procedures	Open Label Follow-Up Period				Early Discontinuation	Notes
	Visit 9	Visit 10	Visit 11	Visit 12		
	Day 17 (+/- 2 day)	Day 24 (+/- 2 day)	Day 31 (+/- 2 day)	Day 38 (+/- 2 days)		
Laboratory Assessments						
Pregnancy Test	D17(u)	D24(u)	D31(u)	D38(u)	ED(u)	(s)= serum; (u) urine. If urine test cannot be confirmed as negative, a serum test is required.
Plasma for HIV-1 genotype/phenotype	.	.	.	.	ED	
Lymphocyte T-cell subsets (CD4, CD8)	.	.	.	D38	ED	
Hematology / Chemistry / Coagulation/ Urine	D17	D24	D31	D38	ED	See Appendix 2, Section 8.3.4 for details of clinical laboratory tests. Includes fasting glucose and fasting lipid panel.
Plasma for storage	D17	D24	D31	D38	ED	Plasma samples for storage will be collected at each outpatient visit starting at Screening 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. See Section 8.8 for more details.
HIV-1 RNA	.	.	.	D38	ED	
Plasma PK sampling	CCI [redacted]					To be collected at the same time as HIV-1 RNA samples (with no preference as to which is drawn first).
Standard of Care ART						
Dispense standard of care ART	D17	D24	D31	D38	ED	Standard of care antiretroviral therapy (SoC ART) will be chosen by the investigator. Choice will be informed by local treatment guidelines, accepted clinical practice and accessibility. If allowed per local regulatory guidelines and desired by participant and Investigator, standard-of-care treatment will be continued for up to an additional 3 months following completion of follow-up assessments (post Day 38)
Adherence counselling	D17	D24	D31	D38	ED	Adherence counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a participant-centered manner, tailored as needed to the information, skills building, and support needs of each participant. Discussions to be documented within site source files.

AE= Adverse Events; (b)= Brief physical exam; ART= antiretroviral therapy; BMI= Body Mass Index; (c)= Complete physical exam; D10= Day 10; D17=Day 17; D24=Day 24; D31=Day 31; D38=Day 38; ECG= electrocardiograph; ED=Early Discontinuation; HIV-1= human immunodeficiency virus type 1; PK= Pharmacokinetic RNA= ribonucleic acid; SAE= Serious Adverse Events: Standard of care antiretroviral therapy (SoC ART)

2. INTRODUCTION

2.1. Study rationale

VH4524184 is a CCI [redacted] INSTI CCI [redacted]. The in vitro antiviral potency of VH4524184 is CCI [redacted] with a likely high genetic barrier to resistance.

This POC study is designed to gain information on the antiviral effect, safety, tolerability and PK properties of VH4524184 orally administered to adults infected with HIV-1 who have yet to initiate treatment.

Clinical development of VH4524184 is ongoing. Study 218803 is an ongoing FTiH study evaluating the safety, tolerability and PK properties of CCI [redacted] VH4524184 in healthy participants and 218804 is a planned FTiH study evaluating the safety, tolerability and PK properties of CCI [redacted] VH4524184 in healthy participants. Study 218803 has shown VH4524184 to be generally well-tolerated in healthy participants to date (63 participants received VH4524184 as of 27 July 2023) and has thus far demonstrated a favorable PK profile suitable for progression to TN adults with HIV-1 in this Phase 2a POC 10-day, monotherapy study, CCI [redacted]

The data gathered from this study, together with data from the ongoing Phase 1 studies CCI [redacted], will inform subsequent clinical trials and Phase 2b clinical development.

2.2. Background

2.2.1. Unmet Medical Need

Globally, approximately 39 million people are currently living with HIV/AIDS. This worldwide epidemic continues to grow at a rate of 1.3 million new infections and causes 0.6 million deaths per year[UNAIDS, 2023]. HIV-1 treatment requires life-long therapy with a minimum of two antiretroviral (ARV) medicines with different mechanisms of action.

Management of HIV chronically is associated with long-term toxicity of anti-retroviral therapy (ART) as well as the possibility of development and transmission of resistant virus. Long-term toxicities may impact the CNS, CV system, alterations in metabolism and impaired renal function. Regimens which avoid particular classes of agents may help avoid or manage comorbidities among persons with HIV (PWH) and the use of treatment regimens with fewer medicines have the potential to reduce long-term toxicities by reducing ARV exposure. Treatment failure remains a continuing concern in clinical care due to the presence and emergence of resistant strains and tolerability issues. In addition, managing an aging population of PWH with an increasing prevalence of comorbidities and polypharmacy requires ARVs with the potential for fewer drug-drug interactions.

ARVs are notably effective, having converted an inevitably fatal infection into a chronic condition, but there is an opportunity for developing more conveniently dosed and better tolerated ARV regimens. There remains on-going need for new ARV agents with improved safety and tolerability. CCI [redacted]

CCI [redacted]

Summaries of the non-clinical studies of VH4524184 and safety and PK clinical data CCI [redacted] of VH4524184 in study 218803 are included in the IB [GSK Document No RPS-CLIN-069016].

The safety and pharmacokinetic profile of CCI [redacted] VH4524184 are being characterized in healthy volunteers in the ongoing study 218803.

2.2.1.1. Study 218803 – CCI [redacted] FTiH VH4524184

Study 218803 is a double-blind (sponsor-unblinded), randomized, placebo-controlled, FTIH study in a combined single- and multiple-dose protocol to investigate the safety, tolerability and PK of VH4524184 in healthy participants [GSK Document Number TMF-16041100]. This study is designed to evaluate:

- the safety, tolerability, and PK properties of VH4524184 when administered as single and multiple ascending dosing CCI [redacted]
- the safety, tolerability, and PK of the VH4524184 CCI [redacted]
- CCI [redacted]
- any effect of VH4524184 on the activity of CYP3A using midazolam as a probe.

Dose-proportional increases in geometric mean plasma concentrations of VH4524184 were observed CCI [redacted], without further increases in exposure following CCI [redacted]. VH4524184 geometric mean observed time to maximum concentration and half-life were CCI [redacted]

CCI [redacted].

Overall, there have been no clinically significant safety findings, SAEs, deaths, trends in vital signs, laboratory parameters, ECG parameters nor discontinuations due to AEs.

Forty-five participants were exposed to single doses of VH4524184 or placebo in the SAD part of the study. Twelve participants experienced a total of 17 AEs, the majority of which were mild in severity, per the Investigator, except for an AE of back pain (moderate). Three participants experienced AEs considered by the Investigator to be related to study drug, these included 2 reports of constipation (1 in CCI [redacted] and 1 in CCI [redacted], both mild in severity per the Investigator) and AEs of eye pain and headache in a participant in the CCI [redacted].

Twenty-seven participants were exposed to VH4524184 or placebo CCI [redacted] in the MAD part of the study. Thirteen participants experienced 21 AEs, all of which were mild, per the Investigator, except for 3 moderate AEs (all unrelated: headache, abdominal pain and rib fracture). One participant experienced 2 AEs of fatigue, which were considered by the investigator to be related to study drug.

CCI [redacted]. The treatment periods were separated by CCI [redacted] washout period. Four participants experienced 6 AEs, all of which were mild. One participant experienced an AE of diarrhea on study Day 1, which was considered by the Investigator to be related to study drug.

2.3. Benefit/risk assessment

Pre-clinical safety assessment studies together with safety and PK clinical data CCI [redacted] of VH4524184 in study 218803, which are summarized in the VH4524184 IB [GSK Document Number [RPS-CLIN-069016], have not highlighted any issues with the potential to impact safety in humans. The clinical parameters which will be monitored throughout the study, as described in the SoA (Section 1.3), are based primarily on ADRs which have been observed CCI [redacted], both during clinical development and from post-marketing experience. For CCI [redacted]

To ensure the overall safety of participants (including, but not limited to, the potential risks as outlined in the table below), this clinical trial will include relatively healthy treatment-naïve adults living with HIV-1 who will be actively monitored by receiving frequent clinical, ECG, and laboratory evaluations during their participation in the trial.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VH4524184 may be found in the IB.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention VH4524184		
Hepatotoxicity	Clinical trials have shown that elevations of liver enzymes and/or hepatitis can potentially occur with CCI [redacted]; these events are uncommon. No hepatotoxic events attributed to VH4524184 were observed in CCI FTIH Study 218803.	Standard Medical Monitoring practices and Clinical Safety Data Review processes including review of relevant emerging data. Use of protocol defined measures to minimize the risk of hepatotoxicity in subjects i.e., specific exclusion criteria based on screening hepatic transaminases (ALT/AST values), detailed liver stopping criteria and toxicity management guidance for suspected DILI or other clinically significant liver chemistry elevations, see Appendix 10.5 for required actions and follow-up assessments in the event of liver stopping criteria having been met). Informed consent forms will include notification of the potential for hepatotoxicity.
Depression (including suicidal ideation and behaviors, particularly in patients with a pre-existing history of depression or psychiatric illness)	Depression and suicidal ideation and behaviors have been observed CCI [redacted]. These events occur particularly in patients with a pre-existing history of depression or psychiatric illness. CCI [redacted]	Participants with 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 will be excluded from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted] provide the evidence for this risk. No psychiatric events were observed in CCI FTIH Study 218803.	Participants in the study will undergo intensive physical exam and laboratory testing. In addition, participants will undergo continuous evaluation for all treatment-emergent adverse events, including those related to depression, anxiety, and suicidal ideation/behavior during their participation in the trial; there are clinical stopping criteria based upon incidence and intensity of treatment-emergent AEs. All participants will be administered the CSSRS questionnaire at screening, Day 10, Day 38, or at Early Discontinuation. In the event of a positive CSSRS (abnormal) response confirmed by the investigator, or other report of suicidal ideation and behavior by the participant at any time during the study, the PI/sub-investigator (SI) will arrange for urgent specialist psychiatric evaluation and management. Informed consent forms will include notification of the potential for depression and suicidal ideation/behavior.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity reactions (HSR)	Hypersensitivity is an uncommon but recognized risk for anti-retroviral regimens containing CCI [redacted], regardless of dose. Hypersensitivity-type reactions have been CCI [redacted]. These reactions were characterized by rash and constitutional findings, and sometimes organ dysfunction, including liver injury. The cases which have been reported in association CCI [redacted] have predominantly presented within angioedema and urticaria. While a casual association with more severe or systemic hypersensitivity reactions has not been identified with CCI [redacted] to date, there remains a theoretical risk of such reactions with or without hepatic symptoms. No events indicative of hypersensitivity were observed in Study 218803.	Standard Medical Monitoring practices and Clinical Safety Data Review processes including review of relevant emerging data from ongoing studies. Participants with history of drug hypersensitivity, delayed-type hypersensitivity or severe hypersensitivity reactions, as well as history of hypersensitivity to the study drugs are excluded (Section 5.2). Specific/detailed toxicity management guidance for HSR is included in the protocol (Section 7.1.6). Informed consent forms will include notification of the potential for HSR.
CCI [redacted]		Co-medications during the monotherapy phase should be limited to those that are medically necessary. Co-medications should be discussed with the ViiV medical monitor.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	
HIV Resistance to VH4524184	There is an intrinsic risk of resistance (genotypic changes or decreased phenotypic susceptibility) to any developmental ARV – particularly when given in monotherapy Prior CCI Proof of Concept studies: Data from the monotherapy studies for CCI [redacted] showed a decline in HIV-1 RNA over the 10 day treatment duration. No CCI resistance associated mutations were observed and no resistance to existing and commercially available classes of antiretroviral medications (e.g., reverse transcriptase or protease inhibitors) was observed. Of note, there is no known cross-resistance between CCI and other classes of ARVs.	This Phase 2a study is limited to 10 days of monotherapy. Doses of VH4524184 in all active therapy Cohorts were selected to ensure that from Day 1 throughout the dosing period, CCI [redacted] Study conduct will ensure strict adherence to criteria addressing concurrent medications.
Effects on embryo-fetal development	Available data from non-clinical studies has not demonstrated any adverse findings. CCI [redacted]	POCBP must use acceptable forms of non-hormonal contraception through to Day 38. POCBP will have pregnancy testing conducted prior to study intervention and during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted] Doses used in the Monotherapy Period have been studied in CCI [redacted] FTIH study 218803. Supportive pre-clinical data CCI [redacted]	Participants who become pregnant after administration of 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.

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 VH4524184 during this study; however, participants will transition to standard of care ART on study Day 10. 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 profile of VH4524184, safety data obtained from VH4524184 study 218803, the established safety profile of other CCI [redacted] and the planned clinical procedures and evaluations in this study, the potential risks to adult participants with HIV-1 who are treatment naïve and otherwise relatively healthy receiving 10 days of VH4524184 monotherapy followed by SOC are low, evaluable, and manageable.

To date, the benefit-risk profile of VH4524184 has been favorable in the clinical development program, with no new key safety concerns identified that would preclude the ongoing investigations.

Considering risk mitigation strategies incorporated into the study protocols or study management, the potential/identified risks with use of VH4524184 are justified by the anticipated benefits; therefore, the benefit-risk profile of VH4524184 supports continued clinical development for the treatment of HIV-1 infection.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
• To evaluate the antiviral activity of orally administered VH4524184 in TN participants with HIV-1 during 10 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 RNA through Day 10.
Secondary	
• To assess the safety and tolerability of orally administered VH4524184	• Incidence of AEs, severity of AEs and proportion of participants who discontinue treatment due to AEs • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameter (ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, albumin and total protein)
• To characterize the pharmacokinetic profile of orally administered VH4524184	As data permits, PK measures that include: • Cmax, • tmax • Concentration on Day 10
• To evaluate any relationship between VH4524184 exposure and change in plasma HIV-1 RNA	• Correlation of VH4524184 PK parameters with maximum plasma HIV-1 RNA change from baseline through Day 10
• To assess the occurrence of emergent genotypic or phenotypic resistance after 10 days of monotherapy with VH4524184	• Genotypic and phenotypic data from baseline (Day 1) and Day 10 will be compared for amino acid substitutions and VH4524184 fold change IC50.
• To assess the immunologic effects of VH4524184 when administered over 10 days in participants living with HIV	• Change from baseline in CD4+ T-cell count to Day 10
Tertiary	
• To further assess the safety and tolerability of orally administered VH4524184	• Post baseline values and changes over time of vital signs, ECG parameters and suicidality scores. • Absolute values, change from baseline and maximum toxicity grade increase from baseline for hematology, coagulation and remaining chemistry panels

3.1. Primary estimand

3.1.1. Antiviral activity

- The primary objective is to evaluate the antiviral activity of orally administered VH4524184 in TN participants with HIV-1 during 10 days of monotherapy. The estimand is described by the following attributes:
- **Population:**

  Overtly healthy (other than HIV-1 infection) treatment naïve individuals
- **Endpoint:**

  Maximum change from baseline (Day 1) in plasma HIV-1 RNA through Day 10
- **Treatment:**
  - VH4524184 or placebo CCI [redacted]
- **Intercurrent events**:
  - Discontinuation of study treatment due to any reason will be addressed using **while on-treatment strategy**, i.e. any HIV-1 RNA data available after study treatment discontinuation day + 1 and prior to starting SOC will be excluded from calculation of max VLD
  - Use of SOC or other antiviral medication prior to Day 10 will be addressed using **while on-treatment strategy**, i.e., HIV-1 RNA collected after initiation of SOC, if for any reason this takes place prior to Day 10, will be excluded from calculation of max VLD
  - Use of prohibited medication will be addressed using **treatment policy strategy**, i.e., any HIV-1 RNA data available after use of prohibited medication will be used in calculation of max VLD
  - CCI [redacted]
- **Population-level summary:**

  Mean of maximum change from baseline in log10 HIV-1 RNA during Days 1-10

Rationale for estimand: Interest lies in evaluating efficacy of orally administered VH4524184 CCI [redacted], or use of prohibited medications and not in combination with other antiretroviral medication.

3.2. Key secondary estimand(s)

3.2.1. Safety and tolerability

- The secondary objective is to assess the safety and tolerability of orally administered VH4524184. The estimand is described by the following attributes:

- **Population:**

  Overtly healthy (other than HIV-1 infection) treatment naïve individuals

- **Endpoints:**
  - Incidence of AEs, severity of AEs and proportion of participants who discontinue treatment due to AEs
  - Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameter

- **Treatment:**

  VH4524184 or placebo CCI [redacted] followed by SOC on Days 10-38

- **Intercurrent events:**
  - Discontinuation of study treatment due to any reason will be addressed using **treatment policy strategy**, i.e. all safety data after study treatment discontinuation will be used
  - Use of SOC medication prior to Day 10 will be addressed using **while on-treatment strategy**, i.e., safety data collected after initiation of SOC, if for any reason this takes place prior to Day 10, will be excluded from monotherapy safety summaries
  - Use of prohibited medication will be addressed using **treatment policy strategy**, i.e., all safety data will be used regardless of the use of prohibited medication
  - CCI [redacted]

- **Population-level summary:**

  AEs:
  - Number and percentage of participants with AEs
  - Number and percentage of participants with AEs by severity grade
  - Number and percentage of participants with AEs leading to study treatment discontinuation

  Liver panel laboratory parameters:
  - Summary statistics (mean, SD, median, min, max, etc.) of change from baseline
  - Number and percentage of participants with maximum toxicity grade increase relative to baseline

Rationale for estimand: Interest lies in evaluating safety and tolerability of orally administered VH4524184 irrespective of study treatment discontinuation, CCI [redacted], or use of prohibited medications and not in combination with other antiretroviral medication.

3.2.2. Pharmacokinetic profile

Another secondary objective is to characterize the PK profile of orally administered VH4524184. The estimand is described by the following attributes:

- **Population:**

  Overtly healthy (other than HIV-1 infection) treatment naïve individuals

- **Endpoints: as data permits**
  - Maximum observed plasma drug concentration (Cmax)
  - Time to maximum observed plasma drug concentration (tmax)
  - Concentration on Day 10
- **Treatment:**

  VH4524184 or placebo CCI [redacted] followed by SOC on Days 10-38

- **Intercurrent events:**
  - Discontinuation of study treatment due to any reason will be addressed using **while on-treatment strategy**, i.e. PK data after study treatment discontinuation will be excluded from use in noncompartmental analyses.
  - Use of SOC medication prior to Day 10 will be addressed using **while on-treatment strategy**, i.e., PK data collected after initiation of SOC, if for any reason this takes place prior to Day 10, will be excluded
  - Use of prohibited medication will be addressed using **treatment policy strategy**, i.e., all PK data will be used regardless of the use of prohibited medication
  - CCI [redacted] of study treatment will be addressed using **while on-treatment strategy**, i.e., PK data collected CCI [redacted] will be excluded from use in noncompartmental analyses.
- **Population-level summary:**

  Summary statistics (e.g. arithmetic mean, SD, median, min, max, geometric mean, SD (log), %CVb, etc.)

Rationale for estimand: Interest lies in characterizing the PK profile of orally administered VH4524184 which could be biased by study treatment discontinuation, CCI [redacted], or use of SOC medication prior to day 10.

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 VH4524184 over 10 days in up to approximately 28 ART naive adults with HIV-1 and detectable viremia.

This study will be conducted in 2 parts. In Part 1, 21 TN participants will be randomized to 1 of 3 cohorts. Within each cohort, 6 participants will receive VH4524184 and 1 will receive matching placebo CCI [redacted]

Part 2 of the study is optional. The conduct of Part 2 is dependent on the informal interim evaluation of the exposure-antiviral response data from Part 1 using available preliminary clinical data from Part 1. Interim analysis of Part 1 will determine if evaluation of a fourth dose of VH4524184 would be informative to properly characterize the exposure-antiviral relationship. If evaluation of a fourth dose is needed, Part 2 will be conducted and will include 1 additional cohort in which up to 6 participants would receive VH4524184 and 1 would receive matching placebo. Part 2 may evaluate 1 additional dose, with the dose and frequency informed by PK/PD modelling of Part 1 data.

In both Part 1 and Part 2, each dose of VH4524184 will be evaluated as double-blind (Sponsor unblinded) monotherapy for 10 days (primary endpoint). On Day 10, participants will start open-label SOC ART that is selected by the investigator and locally sourced. Participants will be followed weekly through Day 38. CCI [redacted]

All participants will be screened for eligibility preferably within approximately 7 to 14 days before being randomized into a 10-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.

Following screening, the study requires a total of 9 in-clinic visits (5 in-clinic visits will occur in the Monotherapy Period; 4 in-clinic visits will occur in the Open Label Follow-up Period) and 3 virtual visits (3 virtual visits will occur in the Monotherapy Period; participant may choose to attend the visit in clinic and this is acceptable). CCI [redacted]

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 1, 2 and 3, and optional cohort 4) 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.

Total duration of study participation is approximately 45 to 66 days based on the following:

- **Screening Period:** 7 to 14 days, with a maximum of 28 days permitted in some cases for screening/qualification period.
- **Monotherapy Period:** 10 days for treatment with the study intervention and assessment at all planned visits.
- **Open Label Follow-up Period:** 28 days for follow up visits while on SOC ART including the final follow up visit.

See Section 1.3 (Schedule of Activities) for additional details of activities during screening, the monotherapy period and the SOC period.

4.2. Scientific rationale for study design

This is a Phase 2a, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled, adaptive design, proof of concept clinical study to evaluate the antiviral effect, safety, tolerability, and PK/PD of 10 days of orally administered VH4524184 monotherapy, an investigational HIV-1 CCI, in ART naive HIV-1 viremic adults.

On Day 10, all participants will switch to standard-of-care antiretroviral therapy selected by the investigator CCI

Though there are commercially available/approved CCI available data suggests that CCI resistance does not occur during short periods of CCI monotherapy; therefore, dosing with VH4524184 will not interfere with selection of the ART regimen selected by the investigator on Day 10 and any subsequent regimen following completion of the study.

The purpose of this study is to evaluate the short-term safety and effect on reducing HIV-1 RNA levels from baseline for different doses of orally administered VH4524184. This study will facilitate an initial understanding of the antiviral activity and safety profile of VH4524184 in an HIV positive ARV naïve adult population, while limiting the monotherapy exposure to reduce the likelihood of development of viral resistance. The data gathered from this study, together with data from the 2 ongoing Phase 1 studies will inform subsequent clinical trials and Phase 2b clinical development CCI

There is an established precedence to use a randomized placebo-controlled short-term monotherapy design in a small number of participants when initially evaluating the activity of new investigational HIV anti-viral agents. This design allows an early understanding of the anti-viral potency and emerging safety profile across different doses while limiting the duration of exposure to the fewest number of HIV-infected participants. The placebo control maintains the blind, reduces bias in the investigator's evaluation and management of safety events, and permits a comparison of safety and efficacy outcomes between the investigational product and placebo.

The 2-part adaptive design will allow for interim evaluation of the exposure-antiviral response data to determine if evaluation of a fourth dose of VH4524184 would be informative to properly characterize the exposure-antiviral relationship. If a fourth dose is not needed, then exposing additional participants to the investigational product can be avoided.

4.2.1. Participant input into design

Community advisors living with HIV were engaged in development of this short-term monotherapy proof-of-concept study design. The group of highly experienced patient advocates provided feedback on protocol feasibility and informed guidance for study implementation (such as considerations for assessment of site facilities, potential services to ease participant burden during longer visits and travel to site, potential inclusion of POCBP in the study population, and considerations for the development of the informed consent document).

4.3. Justification for dose

The pharmacokinetics following CCI VH4524184 has been characterized in study 218803 [IB, 2023]. The CCI cohort in 218803 CCI . Exposures in the highest dosing cohort in this study will be lower than what has been observed in 218803 and based on the tolerability and safety profile in the FTiH CCI study, dosing in the PoC protocol is considered safe. A POP PK model was developed from participant VH4524184 PK observations collected in study 218803. CCI . Details for POP PK model development are described in the 218804 Human Dose Prediction Report [GSK Study report TMF-16733560]. The POP PK model is being leveraged herein to simulate VH4524184 exposures that achieve desired trough concentrations across 3 dosing Cohorts. The in vitro target trough concentration for VH4524184 is CCI . Doses of CCI were selected for this study to establish an in vivo dose-response relationship by targeting typical subject trough concentrations that CCI

Figure 2 Simulated Plasma concentrations of VH4524184 Achieved Following Dosing of CCI

CCI

The maximum reduction of HIV-1 RNA from baseline (~ 2 – 2.5 log10 reduction) has been consistent across CCI [Markowitz, 2006; Min, 2011; Spreen, 2013; Gallant, 2017]. CCI of VH4524184 CCI is anticipated to achieve maximum Day 10 reduction of HIV-1 RNA from baseline for all participants. Depending on the virologic response observed in the three planned cohorts, an additional cohort may be enrolled to further describe the relationship between VH4524184 exposure and HIV-1 RNA levels. In this instance, PK/PD modeling will be used to inform the dose and frequency of the optional Part 2 cohort.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed 10 days of double blind monotherapy, 4 weeks of Investigator chosen SOC and the Day 38 EOS. The EOS 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.

Approximately 28 TN participants who are viremic at baseline (confirmed HIV-1 RNA ≥ 3,000 copies/mL) and have CD4 T-cell counts ≥200 c/µL will be recruited. Part 1 of the study will enroll approximately 21 participants. If Part 2 of the study is conducted, approximately 7 additional participants will be enrolled.

All participants will be screened for eligibility preferably within approximately 7 to 14 days. 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 the screening period lasts beyond 14 days, notification of the medical monitor is required.

5.1. Inclusion criteria

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

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

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. Positive HIV antibody test

4. Documented HIV infection and Screening plasma HIV-1 RNA ≥ 3,000 copies/mL. A single repeat of this test is allowed within a single Screening period to determine eligibility.

5. Screening CD4+ T-cell count ≥200 cells/mm^3

6. Treatment-naïve: No antiretrovirals (ARVs, in combination or monotherapy) received after the diagnosis of HIV-1 infection.

7. HIV Pre-exposure or post-exposure prophylaxis: No prior use of any INSTI (including cabotegravir) for HIV pre-exposure or post-exposure prophylaxis.

8. Body weight ≥50.0 kg (110 lbs.) for men and ≥45.0 kg (99 lbs) for women and BMI within the range 18.5-31.0 kg/m^2 (inclusive - applies to males and females).

9. All participants in the study should be counselled on safe 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.

10. Male or female

    a. Male Participants:

    - No restrictions for male participants

    b. Female Participants:

    - A female participant (female sex assigned at birth) is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
    - Is a PONCBP as defined in Section 10.4.1.1. There is no requirement for PONCBP to use a highly effective method of contraception or complete pregnancy testing.

      OR

    - Is a POCBP and is using a non-hormonal contraceptive method that is highly effective (failure rate of <1% per year when used consistently and correctly) as described in Section 10.4.2, during the study, and through the last visit in the Follow-up Period (Day 38). The Investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

11. A participant of childbearing potential must have a negative serum hCG test at screening, and negative urine hCG test at Day 1, before the first dose of study intervention. See Section 8.3.5, Pregnancy testing.

- If a urine test cannot be confirmed as negative (e.g. ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease risk for inclusion of a female with an early undetected pregnancy.

12. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form and stated in this protocol.

13. Participant must be willing and able to start standard-of-care ART as selected with the investigator on Study Day 10.

5.2. Exclusion criteria

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

5.2.1. Medical Conditions

1. 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.

2. Any evidence of an active CDC Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy during the study.

3. Untreated syphilis infection [positive RPR at screen] without documentation of treatment. Participants who have successfully completed treatment at least 7 days previously are eligible if recruitment is open.

4. 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.

5. Any pre-existing physical or mental condition which, in the opinion of the Investigator, 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. 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 eCSSRS.

7. Any history of major depressive disorder with or without suicidal features, or anxiety disorders, that required medical intervention (pharmacologic or not) such as hospitalization or other inpatient treatment and/or chronic (>6 months) outpatient treatment. Participants with other conditions such as adjustment disorder or dysthymia that have required shorter term medical therapy (<6 months) without inpatient treatment and are currently well-controlled clinically or resolved may be considered for entry after discussion and agreement with the Medical Monitor.

8. CCI [redacted]

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

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 (e.g., prior myocardial infarction, sinoatrial pauses, bundle branch block, or conduction abnormality) which, in the opinion of the Investigator OR ViiV Medical Monitor, will interfere with the safety for the individual participant.

11. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination and will be the screening ECG entered into the eCRF):

	Males	Females
Heart rate[1]	<45 or >100 bpm	<50 or >100 bpm
PR interval	<120 or >200 msec	
QRS duration	<70 or >110 msec	
QTcF interval [2,3]	>450 msec	>470 msec

1 A heart rate from 100 to 110 bpm can be rechecked by ECG within 30 minutes to verify eligibility.

2 QTcF > 480 msec in participants with bundle branch block.

3 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. The specific formula that will be used to determine eligibility and discontinuation for an individual subject will be determined prior to initiation of the study - QTcF will be used for this study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

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

5.2.2. Prior/Concomitant Therapy

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.

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 6.9.1 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 hypersensitivity (including delayed hypersensitivity or severe hypersensitivity reactions) or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

15. Participants who require concomitant medications known to be associated with a prolonged QTc.

16. Participants receiving any protocol-prohibited medication(s) and who are unwilling or unable to switch to an alternate medication (See Section 6.9.2).

5.2.3. Prior/Concurrent Clinical Study Experience

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

18. Exposure to an experimental drug or experimental vaccine within either 30 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.

    - Note: Receipt of a SARS-CoV-2 vaccine that has received emergency, conditional, or standard market authorization is allowed at least 14 days prior to study entry (i.e., Screening) if the Principal Investigator (PI) determines that the benefit-risk profile for that individual study participant is favorable. The use of other investigational COVID vaccines that have not received emergency, conditional, or standard market authorization and are still only used in clinical studies will not be allowed at this time.

19. Participation in the study would result in donation of blood in excess of 500 mL within 56 days.

20. Exposure to more than four new investigational drugs or vaccines within 12 months prior to the first dosing day.

21. Current enrollment or past participation within the last 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research.

5.2.4. Diagnostic Assessments

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 randomization 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. Positive Hepatitis C RNA test result at Screening.
    - Note: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

25. Any Grade 3-4 laboratory abnormality is exclusionary (with the exception of Grade 3-4 CPK and lipid abnormalities (e.g., total cholesterol, triglycerides, etc) following discussion and agreement by Sponsor Medical Monitor). A single repeat of any lab abnormality is allowed within a single Screening period to determine eligibility.

26. Alanine aminotransferase (ALT) > 1.5 x ULN and / or total bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%). A single repeat of ALT and / or bilirubin is allowed within a single Screening period to determine eligibility.

27. Creatinine clearance (eGFR) of < 60 mL/min/1.73 m^2 using CKD-EPI equation (2021)

28. Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.

5.2.5. Other Exclusion Criteria

29. Any positive result for illicit drug use (e.g., cocaine, heroin) at Screening. A positive screen for marijuana / THC is not exclusionary.

30. Heavy use of tobacco or nicotine containing products (≥ 20 cigarettes per day or equivalent, as determined by the investigator).

31. During the study, alcohol consumption will be limited to the following:

    - An average weekly intake of <14 drinks for males or <7 drink for females. 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.

5.3. Lifestyle considerations

5.3.1. CCI and dietary restrictions

- Participants will be required to fast for at least 8 hours (overnight) prior to the morning check-in for the Days 1, 2, 4, 7, 10, 17, 24, 31 and 38/Early Discontinuation Visits.
- Blood work for the safety labs and HIV-1 RNA will be drawn at the beginning of any clinic visit and, when applicable, before consumption of any meal and dosing. See Section 1.3 (Schedule of Activities) and Section 8 (Study Assessments and Procedures) for order of assessments.

CCI [redacted]

- Refrain from excessive consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 3 days prior to the first dose of study medication through the Day 10 visit. Excessive consumption is defined as more than 1 glass of red wine or juice or 1 fruit per day, in combination.

5.3.2. Alcohol and tobacco

- No alcohol consumption is allowed 8 hours prior to each blood collection for clinical laboratory tests and on intensive PK days CCI [redacted] until after the final assessment of the day and release from the clinic. Overall limitations on alcohol consumption are described in Section 5.2.5.

- Only clinically mild to moderate use (< 20 cigarettes per day or equivalent, as determined by the investigator) of tobacco or nicotine containing products will be allowed during study participation, with extremely limited use on the intensive PK days CCI to ensure it does not interfere with appropriate collection of samples, until after the final assessment of the day and release from the clinic.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during study participation.

5.3.4. Other restrictions

Not applicable

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. Screening assessments that yield abnormal results (e.g., a safety laboratory parameter) may be repeated once within the screening window at the discretion of the investigator. Individuals who failed initial screening but passed rescreening may be admitted into the study based upon clinical judgement with consultation with the ViiV medical monitor as necessary.

Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded 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	**VH4524184** CCI	**Placebo to match VH4524184** CCI
Intervention Name	VH4524184 CCI	Placebo to match VH4524184 CCI
Intervention Description	CCI	CCI
Type	Drug	Drug
Dose Formulation	CCI	CCI
Unit Dose Strength(s)	CCI	Not applicable
Dosage Level(s)	Variable depending on dose	Variable depending on dose
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP/AxMP.	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
CCI		
Current alias	GSK4524184	Not applicable

Table 5 Study Arm(s)

Arm Title	VH4518424 CCI	Placebo for VH4524184 CCI	VH4518424 CCI	Placebo for VH4524184 CCI	VH4518424 CCI	Placebo for VH4524184 CCI	VH4518424 CCI	Placebo for VH4524184 CCI
Part	Part 1	Part 1	Part 1	Part 1	Part 1	Part 1	Part 2	Part 2
Arm Type	Experimental	Placebo	Experimental	Placebo	Experimental	Placebo	Experimental	Placebo
Regimen number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Arm Description	CCI [redacted] CCI							

[1] The dose and frequency to be evaluated in Part 2 will be based on preliminary analyses of exposure and response data from Part 1. As a result, the arm description and the placebo to match in Part 2 would then be aligned to the specific dose that is chosen.

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 GSK.

6.3 Assignment to study intervention

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

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

Unused study intervention CCI [redacted] may not be offered to the study participant beyond the expected dosing schedule as outlined in the SoA and may not be offered to any other person.

6.4 Blinding, masking

This is a double-blind (sponsor unblinded) placebo-controlled study in which participants and investigators are blinded to study intervention at a participant level.

The specific intervention to be taken by a participant will be assigned using an IWRS. The site will contact the IWRS prior to the start of study intervention administration for each participant.

Potential bias will be reduced by the following:

6.4.1 Randomization and treatment assignment

All participants will be randomized, according to the randomization schedule generated prior to the study by the Biostatistics Department at GSK using validated internal software. Each participant scheduled to receive study drug will receive a treatment allocation number when randomized.

Participants and investigators will know to which double blinded arms (Cohorts 1, 2, 3 or 4) participants are assigned to.

The blinding strategy for this study is further structured to ensure that no one at VH/GSK who is involved in the management of individual participants is unblinded to treatment at the participant level. As a general principle during study conduct, members of the VH/GSK study team and other VH/GSK staff will remain blinded to the assignment for individual participants aside from where unblinding is necessary to support the informal planned interim analyses or becomes necessary for safety reasons.

Refer to Section 9.4 for more details about preservation of the blind during the conduct of the informal planned interim analyses.

6.4.2 Central Laboratory

The central laboratory in charge of HIV-1 RNA testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

The investigator, site staff and VH/GSK will be unblinded to HIV-1 RNA results performed at screening in order to determine HIV status for eligibility purposes.

The investigator, site staff, and VH/GSK study team members involved in participant management, will be blinded to HIV-1 RNA results during the monotherapy and follow-up periods.

Refer to Section 9.4 for more details about preservation of the blind during the conduct of the informal planned interim analyses.

6.4.3 Emergency unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a 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 VH/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, VH/GSK must be notified

within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If the investigator is unable to access the IWRS 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.

A participant may continue in the study if that participant's intervention assignment is unblinded.

VH/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 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5 Study intervention compliance

CCI [redacted]. The date and time of each dose administered CCI [redacted] will be recorded in the source documents.

6.6 Dose modification

Modifications to the dose are not applicable in this study.

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

Continued access to VH4524184 after the end of the study is not permitted since therapeutic benefit has not yet been established.

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 ART 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 VH4524184 (period: 10 days). On study Day 10, following the scheduled blood collection as per SoA, participants will commence standard-of-care ART 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 ART, 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 ART. 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 if no access barrier) to receive reimbursement from the Sponsor for locally marketed ARVs after the completion of the study (i.e., Day 38 EOS which includes 10 days of double-blind monotherapy and 28 days of investigator chosen SOC) 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:

1. 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.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until VH4524184 can no longer be detected systemically CCI as medically appropriate.
3. Obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the 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.

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 (if an experimental vaccine, within at least 30 days prior to first dose). Please discuss with medical monitor if planning to give vaccines 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 VH 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. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

4. 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

See Section 5.2.2.

CCI

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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 should remain in the study, continue to comply with all other aspects of the protocol (such as starting the first dose of standard of care ART on Day 10) and be followed according to the SoA (Section 1.3) to the EOS as defined in the protocol.

If participants prematurely discontinue study treatment prior to Day 10 (primary endpoint), participants may be replaced at the discretion of the Sponsor in consultation with the investigator.

Participants will not be replaced if the reason for discontinuation from the study treatment is due to a safety concern which the investigator considers reasonably attributable to study treatment e.g., when a participant meets stopping criteria. Refer to Section 7.1.2 (Liver chemistry stopping criteria), Section 7.1.3 (QTc stopping criteria) and Section 7.1.5 (Suicidal ideation and behavior) and Section 7.1.6 (Hypersensitivity reactions).

A participant may be discontinued from the study intervention at any time if any of the protocol individual stopping criteria are met:

- Emergence of any positive (abnormal) CSSRS response, or participant report of suicidal ideation and behavior at any time during the study, confirmed by the investigator or a clinician (or qualified designee) during the monotherapy period.
- Pregnancy
- ≥ Grade 3 AE (or clinically significant laboratory abnormality) suspected to be related to VH4524184.
- An SAE, regardless of its severity, that is considered to be clinically significant and reasonably attributable to dosing with VH4524184, in the opinion of the Investigator.
- A grade ≥2 rash with concurrent fever with or without concurrent elevations in liver biochemistry reasonably attributable to dosing with VH4524184, in the opinion of the Investigator.
- Emergent medical condition that is judged by the Investigator as to jeopardize the subject's safety if he or she continues to receive the study drug.

- Termination of the study by the Sponsor. Safety data will be reviewed by the Sponsor instream by single case and collectively. If a safety concern arises, a decision about continuation of the study will be made.

- Loss of ability to freely provide consent due to incarceration or involuntary treatment of either a psychiatric or physical (e.g., infectious disease) illness.

- Repeat non-adherence by the participant with the requirements of the protocol or treatment (as determined by Investigator in consultation with the Study Sponsor Medical Monitor)

- Clinical criteria for stopping study are met (as outlined below in Section 7.1)

7.1.1 Capturing reason for discontinuation in the eCRF

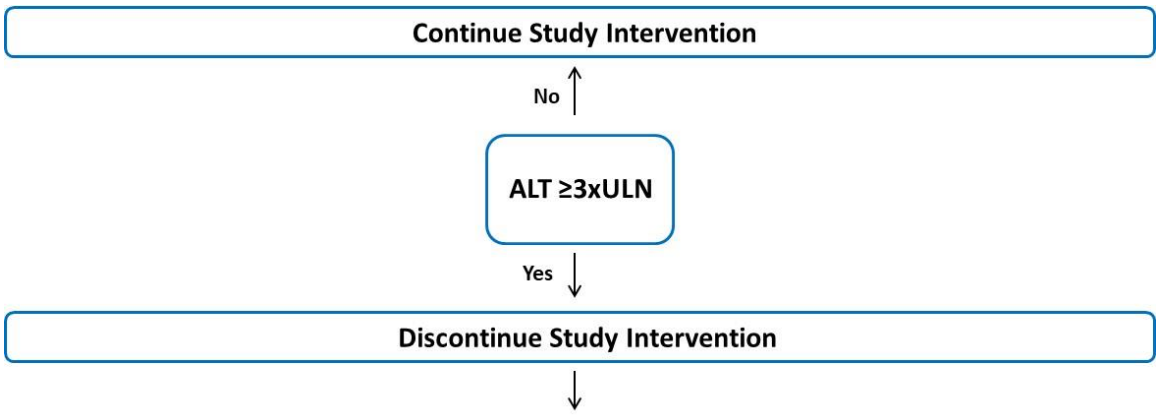
The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	
Lack of efficacy	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Specify
Physician Decision	Specify
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	
Sponsor terminated study treatment	
Study terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pursue Alternative Treatment COVID-19 Pandemic Other
Other	Specify
Death	

7.1.2 Liver chemistry stopping criteria

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Section 10.5 for required Liver Safety Actions and Follow up Assessments

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets 1 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.

Refer to Section 8.3.7 for information about study pausing criteria.

7.1.3 QTc Stopping criteria

The Fridericia QT correction (QTcF) formula will be used in the study.

- A participant that meets either bulleted criterion based on ECG readings will be withdrawn from study treatment.
    - QTcF >500 msec,
    - Change from baseline: QTcF>60 msec
- The QTcF must be used for each individual participant to determine eligibility for, and discontinuation from, the study. This formula may not be changed or substituted once the participant has been enrolled.

- The QTcF stopping criteria is based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in in QTcF >60 msec) after enrollment, the investigator or qualified designee will determine 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.

7.1.4 Pregnancy

Participants who become pregnant during the study should discontinue study drug. Refer to Section 8.4.5 for reporting requirements.

7.1.5 Suicidal ideation and behavior

Participants who experience a confirmed positive eCSSRS, or who report suicidal ideation and/or behavior at any time during the study, should have study drug withdrawn and should be referred for further medical assessment and treatment as appropriate. The participant should be encouraged to continue in the study and be followed as per the SoA (See Section 1.3)

See Section 8.3.6, Suicidal ideation and behavior risk monitoring, for additional guidance.

7.1.6 Hypersensitivity reactions Stopping Criteria

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

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

7.1.7 Temporary discontinuation

Temporary discontinuation of VH4524184/placebo is not allowed in this study.

7.1.8 Rechallenge

Rechallenge with VH4524184/placebo is not allowed in this study.

7.1.8.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are 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 from the study at any time at the discretion of the investigator for safety, behavioral, or adherence reasons. Discontinuing from the study for safety reasons should be infrequent.

As described in Section 7.1, participants who meet a safety stopping criteria or who discontinue study intervention due to a safety reason, should remain in the study, continue to comply with all other aspects of the protocol (such as starting the first dose of standard of care ART on Day 10) and be followed according to the SoA (Section 1.3) to the EOS as defined in the protocol.

Participants will not be replaced if the reason for discontinuation from the study is due to a safety concern.

If participants prematurely discontinue the study for non-safety reasons prior to Day 10 (primary endpoint), additional replacement participants may be enrolled at the discretion of the sponsor and investigator. These replacement participants will be assigned to the same treatment sequence and same dose as the corresponding participant who prematurely discontinued from the study.

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 early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. 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	
Lack of efficacy	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Specify
Physician Decision	Specify
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pursue Alternative Treatment COVID-19 Pandemic Other
Other	Specify
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 10.3.6.5).

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 Section 1.3. Protocol waivers or exemptions are not allowed.
- 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 (e.g., HIV RNA (viral loads) 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 or any 56 day period while enrolled in the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Pharmacokinetic results that could unblind the study will not be reported to investigative sites or other blinded personnel.
- **Order of assessments:** Assessment procedures should occur in the following order:

1. ECG (if applicable)
2. Vital sign assessment
3. CSSRS
4. Blood draws; (HIV RNA to be collected at same time as pre-dose PK sample [with no preference as to which is drawn first])
5. CCI [redacted]

- All Day 10 assessments must be completed prior to administration of the first dose of standard of care ART.

8.1 Administrative and baseline procedures

8.1.1 Collection of demographic data

Record demographic data such as year of birth, sex at birth, current sex, current gender identity, race, and ethnicity in the participant's eCRF.

Collection of these demographic 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/vaccination history

Obtain the participant's medical and disease history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions (including reasons for taking concomitant medications), signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

8.2 Efficacy assessments

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

8.2.1 Quantitative HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected at timepoints listed in Section 1.3. An HIV-1 RNA PCR assay (Cobas HIV-1) with a linear range of 20 to 10,000,000 copies/mL will be used. Details concerning the handling, labeling and shipping of these samples to the central laboratory will be supplied in the Laboratory Manual.

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 Section 1.3. Details concerning the handling, labeling and shipping of these samples will be supplied in the Central Laboratory Manual. Refer to the List of Clinical Laboratories and Key Vendors document for laboratory names and addresses of the clinical laboratories used in this study.

8.3 Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1 Physical examination/history directed physical examination

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). At the discretion of the investigator, a brief physical examination may be made a complete physical examination.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Height and weight measurements will be used to calculate BMI.

8.3.2 Vital signs

- Body temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
- Body temperature will be assessed as per site's standard practice and should be measured at the same location throughout the study.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions. Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- If abnormalities in pulse or blood pressure are noted, repeat recordings should be measured in triplicate, at least 1 minute apart. The average of the 3 readings will be recorded in the eCRF.

8.3.3 Electrocardiograms

- 12-lead ECG(s) 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 [QTc] intervals. Each ECG recording will be obtained after the participant has been in a semi-supine position for at least 5 minutes. The ECG should be read locally. Contact the VH medical monitor with any concerns.
- If clinically indicated, the ECG should be repeated twice more (triplicate obtained) with recordings obtained as closely as possible in succession. Data from the average of 3 ECGs will be used for any action taken. Triplicate ECGs should be obtained if the investigator determines an ECG abnormality is clinically significant or if the investigator is unable to determine the significance of abnormalities relating to rate, rhythm, or intervals (including prolongation of the QT interval),
- Refer to Section 7.1.3 for QTc stopping criteria for further details.

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 from dosing of the study intervention until EoS visit (i.e., Day 38) 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), then the results must be recorded.

8.3.5 Pregnancy testing for participants of childbearing potential

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Refer to Section 1.3 (Schedule of Activities) for pregnancy testing schedule.
- POCBP must perform a pregnancy test before the administration of any dose of study intervention during the Monotherapy Period. Pregnancy testing will continue throughout the Follow-up Period.
- Serum samples will be sent for pregnancy testing for the Screening Visit. At the Day 1 Visit (before start of study treatment), a urine test must be used to confirm pregnancy status prior to administration of study treatment.
- Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

- Refer to Section 8.4.5 (Pregnancy reporting) for pregnancy reporting requirements and information on study continuation for participants who become pregnant during the study.

8.3.6 Suicidal ideation and behavior risk monitoring

Although VH4524184 is not being developed for a neurologic or psychiatric condition, participants will be excluded based on any pre-existing psychiatric condition (including assessment using the CSSRS). Depression (including suicidal ideation and behaviors, particularly in patients with a pre-existing history of depression or psychiatric illness) are adverse drug reactions CCI [redacted].

Participants receiving VH4524184 should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and the participant should not receive any additional doses of VH4524184.

Assessment of suicidal ideation and behavior / intervention emergent suicidal ideation and behavior will be monitored using the electronic CSSRS (see SoA, Section 1.3 for details) at Screening, on Day 10 and the final follow-up visit, as well as at early termination, if applicable. As described in Section 7.1, any positive (abnormal) CSSRS response indicating SIB, or SIB reported by the participant at any other time during the study, will result in withdrawal of study drug. In either case (screening or post-dose) of positive (abnormal) response confirmed by the investigator, the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. A response graded as level 4 or 5 for suicidal ideation and/or any positive response to questions addressing suicidal behavior is considered a positive CSSRS which then should be confirmed by the investigator following an interview with the participant.

Participants who experience a confirmed positive CSSRS, or who report SIB at any other time during the study, should have study drug withdrawn and should be referred for further medical assessment and treatment as appropriate. The participant should be encouraged to continue in the study and be followed as per the SoA. (See Section 1.3).

Additionally, the investigator will collect information using the PSRAE eCRF form in addition to the AE (non-serious or SAE) eCRF form on any subject 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 his or her medical and scientific judgment in deciding whether an event is possibly suicide related. PSRAE forms should be completed and reported to VH/GSK within 1 week of the investigator diagnosing a possible suicidality-related AE.

8.3.7 Study pausing rules

Participant safety will be continuously monitored by the Medical Monitor, 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. The Sponsor's governance group, VSLC will review data and the team's recommendation when any pausing/stopping rules are met. The VSLC is comprised of senior representatives from various departments, including clinical development, safety, toxicology, pharmacovigilance, epidemiology, and medical affairs. The VSLC will govern whether enrollment may be resumed/modified, a given treatment arm will be stopped, or the study stopped. (See Section 10.1.6 for more details on VSLC)

The following study pausing criteria would be applied:

- Death of a participant, regardless of investigator's assessment of causality
- Any Grade 4 event or an SAE, regardless of its severity, that is considered to be clinically significant and reasonably attributable to dosing with VH4524184 in the opinion of the investigator or the Sponsor.
- Any Grade 3 or higher AE (of the same type) in 2 or more participants, leading to the decision to withdraw from the study (by the investigator), assessed by the investigator as reasonably attributable to VH4524184.
- Any Grade 2 or higher rash with evidence of systemic involvement (e.g., fever, liver transaminase elevation and/or eosinophilia) that the investigator considers reasonably attributable to VH4524184 occurring in two or more participants.
- Any Grade 4 laboratory abnormality (of the same type) or Grade 3 laboratory abnormalities (of the same type, with the exception of an asymptomatic Grade 4 lipid abnormalities or CPK increase) that the investigator considers reasonably attributable to VH4524184, in two or more participants.
- Any participant meeting liver stopping criteria that the investigator considers reasonably attributable to VH4524184.
- Any participant meeting QTc stopping criteria that the investigator considers reasonably attributable to VH4524184.
- Clinically significant arrhythmia in two or more participants.

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 intervention or 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 (AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting), and/or Section 10.6 (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events).

8.4.1 Time period and frequency for collecting AEs and SAEs

All SAEs will be collected from the signing of the ICF until the final follow-up visit. Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 and/or Section 10.7. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 10.3.6.

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 10.3.6.5.

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 10.3.6.3.
- 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 reporting

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 treatment in the Monotherapy Period (Day 1) and until the final visit in the Follow-up Period (Day 38). Report all pregnancies to the Medical Monitor.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form (initial notification form or pregnancy follow-up form) and submit it to the sponsor within 24 hours of learning of the female participant's pregnancy (see Section 10.3.7).
- 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. See Section 10.3.7 for reporting timeframes.
- 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 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- All investigators are strongly encouraged to report all pregnancies exposed to standard of care ART to the Antiretroviral Pregnancy Registry (APR) as soon as the pregnancy is identified. Pregnancies can be reported to the Registry at SM_APR@APRegistry.com via the data forms available at www.APRegistry.com.

8.4.6 Cardiovascular events and death events

For any CV events detailed in Appendix Section 10.3.4 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 1 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 1 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 events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.7) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to VH/GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part ‘f’ of the SAE definition (Section 10.3.2), or
- The event or outcome is in the investigator’s opinion of greater intensity, frequency or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to study intervention.
- 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.
- If any of the above conditions are met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF.

8.4.8 Contact information for reporting SAEs and study holding rules

Table 6 Contact information for reporting SAEs and study holding rules

Safety Topic	Contact
Reporting SAEs	Email uk.gsk-rd-gcsp-ctsm-admin@gsk.com Available 24/24 hours and 7/7 days
Questions regarding SAEs	Contact the VH medical monitor
Questions regarding any other safety event that may meet a safety stopping criteria	Contact the VH medical monitor

8.4.9 Participant card

The investigator (or designee) must provide the participant/participant's LAR(s) with a "participant card" containing information about the clinical study. The participant/participant's LAR(s) 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/LAR/caregiver/family member 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

- Intensive and single PK sampling is pre-specified as per the SoA (Section 1.3).

CCI [redacted]

- Otherwise on single PK draw days CCI [redacted] a single PK sample will be drawn in conjunction with the study visit and as close to an every 24-hour post last dose cycle as possible.
- Collected PK samples may not be analyzed if concentrations below the limit of quantification were previously achieved or if the participant was assigned to placebo.
- Refer to Table 7 for the permissible windows CCI [redacted], dosing and PK draws for intensive PK days.

Table 7 Intensive Pharmacokinetic Sampling CCI [redacted]

	Time of Event	Window	Time Relative to Dosing Hour:Minute
Dosing Day	CCI [redacted]	Not applicable	CCI [redacted]
	Pre-dose PK collection	Not applicable	Collect pre-dose sample prior to dosing. There is allowance to collect the sample earlier and up to 90 minutes prior to dosing
	Administer study treatment and start the clock for subsequent blood draws.	Not applicable	00:00
	CCI [redacted]		
CCI [redacted]			

- Instructions for the collection and handling of biological samples will be provided by the sponsor and central laboratory.
    - Blood samples of approximately 2 mL will be collected and processed to plasma for measurement of plasma concentrations of study intervention.
    - The actual date and time (24-hour clock time) of each sample will be recorded.
    - Samples to be stored in an upright position at -70°C or colder until shipment to the test laboratory. Refer to the List of Clinical Laboratories and Key Vendors document for laboratory names and addresses of the clinical laboratories used in this study.
- A maximum of 2 mL 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 study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Plasma samples will be used to evaluate the PK concentrations of VH4524184 and may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 Pharmacodynamics

See Section 8.2 and Section 8.5 for relevant efficacy and PK assessments.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Plasma samples for exploratory resistance testing will be collected according to the schedule described in Section 1.3 and as detailed in the Laboratory Manual. Resistance results will not be available in time to inform the treatment management of participants during the study. Samples from Day 1 (pre-dose) and Day 10 will be batch tested for viral genotypic and phenotypic on treatment changes and/or resistance to the CCI using the Monogram Biosciences Inc. based assays. Plasma from additional timepoints may be assayed if needed.

Additional blood samples may be drawn for local genotypic/phenotypic analysis, according to local guidelines. These tests are optional and will be conducted in accordance with local guidelines for the management of HIV-1 infection and, if available, may be used to guide the choice of standard of care ART. Locally obtained genotypic/phenotypic results will be retained in the participant's medical record at the site and will not be transferred to VH/GSK.

VH/GSK may store samples for up to 20 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by VH/GSK or others such as universities or other companies to contribute to the understanding of HIV-1 or other diseases, the development of related or new treatments, or research methods.

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Health economics or medical resource utilization and health economics

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

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan (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. If methods in the SAP differ from the methods described in the protocol, the SAP will be followed.

9.1 Statistical hypotheses

The primary objective 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 the monotherapy period.

9.2 Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study. • The screened, enrolled and randomized populations must be nested, i.e. the enrolled population must be a subset of the screened population, the randomized population must be a subset of the enrolled population.	• Study Population
Safety	• All participants who received at least 1 partial or full dose of study intervention. • Participants will be analyzed according to the study intervention they actually received.	• Safety
Full Analysis Set (FAS)	• All randomized participants who received at least 1 full dose of study intervention. • Data will be reported according to the randomized study intervention.	• Efficacy
Per-protocol (PP)	• All participants in the FAS for whom there were no major protocol deviations that impact the primary analyses. • Data will be reported according to the study intervention actually received. • Specific details of major protocol deviations that would exclude participants from the PP analysis set will be provided in the SAP.	• Efficacy

Analysis Set	Definition / Criteria	Analyses Evaluated
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	• PK

9.3 Statistical analyses

9.3.1 General considerations/definitions

Data will be summarized by study intervention and dose level, unless otherwise specified.

Data will be summarized either by visit or separately for the monotherapy period and overall (i.e., monotherapy period plus SOC period), as appropriate for each endpoint, unless otherwise specified.

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

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 %CVb may also be used.
- Categorical data: number and percentage of participants

9.3.2 Primary endpoint/estimand analysis

See Section 3.1 for definition of primary endpoint/estimand.

9.3.2.1 Definition of endpoint/estimands

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 monotherapy period in the original and $\log_{10}$ scales. Maximum change from baseline during the monotherapy 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 $\log_{10}$ scales. The $\log_{10}$ transformation is used to allow for direct comparisons with data from other compounds publicly available in the same scale, and hence aid in interpretation.

9.3.2.2 Main Analytical Approach

The primary efficacy analysis will be based on the Full Analysis Set.

Maximum change from baseline in plasma HIV-1 RNA during monotherapy will be summarized by study intervention and dose level, in original and $\log_{10}$ scales.

In addition, change from baseline in plasma HIV-1 RNA at each assessment time point during monotherapy will be summarized by study intervention and dose level, in original and $\log_{10}$ scales.

For participants who withdraw from study prior to the end of monotherapy 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

A supplementary analysis could be conducted to summarize maximum change from Baseline and change from baseline by visit in plasma HIV-1 RNA during the monotherapy period based on the Per Protocol analysis set. Details will be provided in the SAP.

9.3.3 Secondary endpoints/estimands analyses

See Section 3.2 for definition of secondary endpoints/estimands.

9.3.3.1 Safety analyses

All safety analyses will be performed on the Safety analysis set. Safety data will be presented in tabular format and summarized descriptively according to GSK's IDSL.

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

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

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.

Pharmacokinetic analysis will be the responsibility of the CPMS Department at GSK. Plasma 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. Individual plasma PK parameters for each participant will be determined, including but not limited to Cmax and tmax.

Data summaries of plasma concentration and pharmacokinetic parameter data will be the responsibility of Clinical Statistics. Plasma concentrations will be presented in graphical form and will be summarized descriptively by dose level. PK parameters will be summarized descriptively by dose level.

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

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

9.3.3.3 Pharmacokinetic-Pharmacodynamic analyses

Pharmacokinetic-pharmacodynamic analyses will be the responsibility of the CPMS Department at GSK. The relationship between selected PK parameters (e.g., concentrations on Day 10) and selected PD parameters (e.g., maximum change from baseline in log10 plasma HIV-1 RNA) will be explored graphically. Where relationships are apparent, exposure-response models will be used to characterize the relationship and assess the impact of covariates. The details of such exposure-response analysis will be outlined in a separate CPMS analysis plan and may be presented separately from the main study report.

9.3.3.4 Virology analyses

Genotypic assessments will be analyzed separately by the study virologist.

9.3.3.5 Immunology analyses

The immunology analyses will be performed using the safety analysis set. Change from baseline in CD4+ T-cell count will be summarized descriptively.

9.3.4 Exploratory endpoints/estimands analysis

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

9.4 Interim analysis

An informal planned interim analysis will be conducted after all participants in Part 1 have completed their monotherapy period.

The planned interim analysis will evaluate the PK and pharmacodynamic (antiviral activity) of VH4524184 and inform the need for Part 2, as well as future clinical development of VH4524184.

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

The final EoS analysis will be conducted after the completion of the study (i.e., when all participants complete the SOC period on Day 38 visit) and final datasets authorization. At the EoS analysis all primary, secondary and exploratory objectives will be evaluated with two exceptions: the analysis of the viral resistance and pharmacogenetics (if done) may be evaluated at a later stage and each of these outcomes reported separately.

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 viral load decline data from 2 previous POC studies investigating CCI [Min, 2011; Spreen, 2013] we assumed the maximum VLD from baseline in log10 scale for

individual participants follows a normal distribution. The expected precision of the estimated maximum VLD in log10 scale, measured by the 95% CI width, under various sample sizes and assumed data variability (reflected by the sample SD) is shown in the table below.

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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 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.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. 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.

In case of unexpected pregnancy, the participant must be informed that PI such as date of birth and sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4 Recruitment strategy

Participants will be recruited into this study using a variety of methods, including but not limited to: investigators existing databases, local advertising, digital recruitment campaigns, and online prescreening and referral to site. Recruitment materials will be reviewed and approved by the IRB/IEC before use.

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.
- VH/GSK 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.

10.1.6 Committee structure

Participant safety will be routinely monitored by the VH medical monitor and the GSK safety lead(s). Pertinent findings and conclusions are shared with the product's SRT for periodic review of the overall benefit risk profile of the product and escalated, as necessary to VSLC.

An SRT is in place for each VH product. It comprises of a global cross-functional VH/GSK team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual blinded assessment of incoming new efficacy, safety and PK information. An external data and safety monitoring committee is not utilized in this study due to the relatively small size and early phase of the trial. This is further supported by the lack of significant safety findings from the available pre-clinical toxicity studies and preliminary clinical study of VH4524184.

VSLC is a governance group that will review data and the team's recommendation when any pausing/stopping rules are met. The VSLC will govern whether enrollment may be resumed/modified, a given treatment arm will be stopped, or the study stopped. The VSLC is comprised of senior representatives from various departments, including clinical development, safety, toxicology, pharmacovigilance, epidemiology, and medical affairs.

ViiV Healthcare has transferred certain sponsor obligations (e.g., clinical operations, study intervention management, data management, statistics and programming, clinical pharmacology and modelling and simulation, regulatory, pharmacovigilance, etc.) to GSK who are supporting VH in the conduct of this study.

Refer to the List of Clinical Laboratories and Key Vendors document for the names and addresses for the clinical laboratories, contractors and subcontractors used by VH in this study.

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 VH Clinical Study Register in compliance with applicable regulations/VH policy. VH/GSK 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, VH/GSK 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. VH/GSK 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.
- VH/GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- VH/GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

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 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.

- 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.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for 25 years**.**

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 source data acknowledgment or monitoring guidelines.
- 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

VH/GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of VH/GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (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 clinical safety laboratory tests detailed in Table 9 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.
- 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 9 Protocol-required safety laboratory tests

Laboratory Tests	Parameters	
Hematology	▪ Platelet count	
	▪ Red blood cell (RBC) count	
	▪ RBC indices	▪ Mean corpuscular volume (MCV) ▪ Mean corpuscular hemoglobin (MCH) ▪ %Reticulocytes
	▪ WBC count with differential:	▪ Neutrophils ▪ Lymphocytes ▪ Monocytes ▪ Eosinophils ▪ Basophils
	▪ Hemoglobin	
	▪ Hematocrit	

Laboratory Tests	Parameters	
Clinical chemistry[1]	▪ Blood urea nitrogen (BUN)/Urea ▪ Potassium ▪ Creatinine[2] ▪ Sodium ▪ Bicarbonate ▪ Magnesium ▪ Phosphate ▪ Calcium ▪ Glucose (fasting) ▪ Creatine phosphokinase (CPK)[5]	▪ Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) ▪ Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ▪ Alkaline phosphatase[3] ▪ Total bilirubin ▪ Direct bilirubin[4] ▪ Total protein ▪ Amylase
	▪ Lipase (fasting)	▪ Fasting lipid panel (cholesterol, triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL])
Coagulation	▪ Prothrombin time (PT) ▪ Partial thromboplastin time (PTT) International normalized ratio (INR)	

Routine urinalysis	▪ Specific gravity
	▪ pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	▪ Microscopic examination (if blood or protein is abnormal)
	  ▪ Epithelial cells
	  ▪ Red Blood cells
	  ▪ WBC
	  ▪ Casts
	  ▪ Crystals
	  ▪ Culture (if positive: specify pathogen)	

Laboratory Tests	Parameters
Other screening tests	▪ Follicle stimulating hormone and estradiol (as needed in PONCBP only [See Section 10.4.1] Contraceptive and barrier guidance - Definitions) ▪ Highly sensitive (serum or urine) human chorionic gonadotropin (hCG) pregnancy test participants female at birth.[See Section 1.3, Schedule of Activities] ▪ Serum or urine alcohol, cotinine, and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) ▪ Serology [(HIV antibody 4th generation test, HBsAg, and HCV antibody Hepatitis B surface antibody (anti-HBs) and if indicated hepatitis B DNA (by PCR), and hepatitis C virus antibody)], with reflex to HCV RNA (by PCR) if positive. ▪ Syphilis positive rapid plasma reagin (RPR)

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Section 10.5: Liver Safety: Suggested Actions and Follow-up Assessments. All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to VH/GSK in 24 hours (excluding studies of hepatic impairment or cirrhosis).
2. To assess the kidney function, use the CKD-EPI equation (2021).
3. If alkaline phosphatase is elevated, consider fractionating.
4. Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN
5. Recommend repeat testing if CPK is elevated to ensure the result is transient or due to exercise. 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.

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 SRT on a routine basis. However, if 1 or both of the following conditions apply, then the event should be reported promptly to VH/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 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. Is a suspected transmission of any infectious agent via an authorized medicinal product
h. **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 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). 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.

10.3.4 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

10.3.5 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.

10.3.6 Recording assessment and follow-up of AEs, SAEs and pregnancies

10.3.6.1 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 VH/GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by VH/GSK. In this case, all participant identifiers, with the exception of

the participant number, will be redacted on the copies of the medical records before submission to VH/GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.6.2 Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories according to the DAIDS toxicity scales (refer to Section 10.6).

- 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 1 of the severity categories described in the functional DAIDS table shown in Section 10.6.
- **Note:** An event is defined as 'serious' when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE.
- **Note:** Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary.

10.3.6.3 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 VH/GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to VH/GSK.
- The investigator may change 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.

10.3.6.4 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).

10.3.6.5 Follow-up of AEs, SAEs or pregnancies

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by VH/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide VH/GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to VH/GSK within 24 hours of receipt of the information.
- After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

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 end of the study or until the participant is lost to follow-up.

If a participant dies during their participation in the study or during a recognized follow-up period, VH/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 VH/GSK using the paper 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 VH/GSK as described in the Section 10.3.6.7.

10.3.6.6 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 8.4.8.

10.3.6.7 Reporting of SAEs and pregnancies

SAE Reporting to VH/GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to VH/GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- 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 VH 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 GSK non-IMP they will report these events to GSK or to the concerned competent authority (CA) 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 VH/GSK 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 VH medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.3.7 Timeframes for Reporting SAEs, PSRAEs, Pregnancy, and Liver Events

Table 10 Timeframes for Reporting SAEs, PSRAEs, Pregnancy, and Liver Events

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Timeframe**	**Documents**	**Timeframe**	**Documents to be Updated**
All SAEs	24 hours	SAE eCRF [a]	24 hours	SAE eCRF [a]
Possible Suicidality Related Adverse Event (SAE)	SAE eCRF[a] 24 hours	SAE eCRF [a]	SAE eCRF[a] 24 hours	SAE eCRF [a]
	PSRAE eCRF and Form 1 week	PSRAE eCRF and Form	PSRAE eCRF and Form 1 week	PSRAE eCRF and Form
Possible Suicidality Related Adverse Event (AE)	1 week	AE eCRF	1 week	AE eCRF
		PSRAE eCRF and Form		PSRAE eCRF and Form
Pregnancy	24 hours	Pregnancy Initial Notification Form	24 hours	Pregnancy Follow-up Form
ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct)[d] or international normalized ratio (INR) >1.5	24 hours [b]	SAE eCRF [a]	24 hours	SAE eCRF [a]
		Liver Event eCRF [c]		Liver Event eCRF [c]
		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]

a. See Section 10.3.6.7 Reporting of SAE to ViiV Healthcare/GSK. For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality. If the electronic system (eCRF) is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours. Paper reports will be dated and signed by the investigator (or designee).
b. The Medical Monitor must be contacted at onset of liver chemistry elevations to discuss participant safety.
c. Liver event documents (i.e., “Liver Event eCRF” and updates, “Liver Imaging eCRF” and/or “Liver Biopsy eCRF”, as applicable) should be completed as soon as possible.
d. All events of ALT≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants.
e. Complete and submit SAE eCRF if applicable.

10.4 Appendix 4: Contraceptive and barrier guidance

10.4.1 Definitions

10.4.1.1 Participants of childbearing Potential (POCBP)

Participants in the following categories are considered POCBP (fertile):

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Note: Menarche is the first onset of menses in a young participant assigned female at birth. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2 Participant of Nonchildbearing Potential (PONCBP)

Participants in the following categories are considered PONCBP:

1. Premenarchal: Tanner stage 1 (prepubertal)
2. 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.

3. 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 1 FSH measurement (>40 IU/L or mIU/mL) is required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT for at least 3 months to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception guidance

Participants of childbearing potential must agree to use contraception/barrier as detailed below:

NON-HORMONAL CONTRACEPTIVES[a] ALLOWED DURING THE STUDY FOR POCBP INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• IUD
• Bilateral tubal occlusion
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5 Appendix 5: Liver safety: suggested actions and follow-up assessments

Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology

Liver Chemistry Stopping Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report as an SAE[1,2,3].</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to VH medical monitor within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column
• Do not restart or rechallenge participant with study intervention
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)
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 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND total bilirubin < 2xULN</td><td>• Viral hepatitis serology[3]
• Syphilis screening
• Drugs of abuse screen, including alcohol
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, documenting the date and time of the most recent VH4524184 dose[4]
• Obtain serum CPK, LDH, GGT, GLDHand serum albumin
• Fractionate bilirubin, if total bilirubin ≥1.5xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever or rash 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</td></tr>
</table>

Liver Chemistry Stopping Criteria	
and INR ≤1.5: • Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24-72 hours • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	• 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 done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout). The site must contact the VH medical monitor when this test is required. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form and/or Liver Biopsy eCRF forms. o In participants when serology raises the possibility of 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.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ³3xULN and total bilirubin ³2xULN (>35% direct bilirubin) or ALT ³3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody
4. 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. 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 lab manual

5. Liver biopsy may be considered and discussed with local specialists if available, for instance:

    - In participants when serology raises the possibility of AIH
    - In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention
    - In participants with acute or chronic atypical presentation.

10.6 Appendix 6: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1, July 2017

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 Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

- 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).

10.6.1 Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as **Grade 5**

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

10.6.2 QTc prolongation using the Fridericia formula

The DAIDS AE Grading Table provides grading for QTc prolongation using the Bazett formula. When the Fridericia formula is used, QTc prolongation should be graded as shown:

Severity Grade 1	460 msec or greater but less than 480msec
Severity Grade 2	480 msec or greater but less than 500 msec
Severity Grade 3	500 msec or greater OR 60 msec or greater than baseline AND 480 msec or greater
Severity Grade 4	Life-threatening consequences (e.g., Torsades de Pointes, other serious ventricular dysrhythmias)

10.7 Appendix 7 : CDC Classification for HIV-1 Infection

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 esophagus
- 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 esophagitis (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 septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

Source: [CDC, 2014]

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