CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	VH4004280 (also known as GSK4004280) VH4011499 (also known as GSK4011499)
Other Study Interventions	Not applicable
Study Identifier	218307
EU CT Number	2023-505350-18-00
Approval Date	08 May 2023
Title	A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Phase 2a Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Orally Administered Investigational Capsid Inhibitor Monotherapy in HIV-1 Infected Treatment-Naïve Adults
Compound Number/Name	VH4004280 (also known as GSK4004280) VH4011499 (also known as GSK4011499)
Brief Title	Proof of concept treatment study of orally administered VH4004280 or VH4011499 in HIV-1 infected adults
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 In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Senior Vice President, Head of Research & Development. This study is sponsored by ViiV Healthcare. GSK is supporting ViiV Healthcare in the conduct of this study.
Sponsor signatory	Scott McCallister, MD Vice President and Head, Physician Center of Excellence ViiV Healthcare

VH 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 (VH) and GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the VH 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 VH/GSK and the express physical and/or digital informed consent of the participant and/or the participant's LAR.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of VH/GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. VH/GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

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

Study identifier	218307
EU CT number	2023-505350-18-00
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Title	A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Phase 2a Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Orally Administered Investigational Capsid Inhibitor Monotherapy in HIV-1 Infected Treatment-Naïve Adults
Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS AND TRADEMARKS

Abbreviation	Definition
%CVb	Between participant coefficient of variation expressed in percentage
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HBc	Negative status for hepatitis B core antibody
Anti-HBs	Negative status for hepatitis B surface antibody
ARV	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-t)	Area under the plasma concentration time curve from time zero to the last quantifiable time point
AUC(0-24)	Area under the plasma concentration vs time curve from time zero to 24 hours
AUC(0-tlast)	Area under the plasma concentration vs time curve from time zero hours to the time of last quantifiable concentration
AUC(0-inf)	Area under the plasma concentration vs time curve from time zero hours to infinity
AUC(0-τ)	Area under the plasma concentration vs time curve over a dosing interval from time of dosing to the time of the subsequent dose
BLQ	Below the limit of quantification
CCI [redacted]	
CAI	Capsid inhibitor
cART	Combination antiretroviral therapy
CFR	Code of Federal Regulation
CI	Confidence interval
CIB	Clinical investigator's brochure
CIOMS	Council for international organizations of medical sciences
C_{max}	Maximum observed plasma concentration
CPK	Creatine phosphokinase
CPMS	Clinical pharmacokinetics modeling and simulation
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
CSR	Clinical study report
DBL	Database lock
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EoS	End of study
F	Bioavailability

Abbreviation	Definition
FDA	Food and drug administration
FSH	Follicle stimulating hormone
FTiH	First-time-in-human
FU	Follow-up
g	gram
g/L	Gram per liter
GCP	Good clinical practice
GCSP	Global clinical safety and pharmacovigilance
GERD	Gastroesophageal reflux disease
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
h	Hour
Hb	Hemoglobin
HbcAb	Hepatitis B core antibody
HBV or HCV	Hepatitis B or C virus
HbsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IC90	Concentration of drug required for 90% inhibition of the viral replication
ICE	Intercurrent events
ICF	Informed consent form
ICH	International council on harmonization
IDSL	Integrated data standards library
ICSR	Individual case safety reports
IEC	Independent ethics committee
Ig	Immunoglobulin
IM	Intramuscular
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
Kg	Kilogram
LAI	Long acting injectable
lbs	Pounds
m	Meter
MAD	Multiple ascending dose
Max	Maximum
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	Milligram

Abbreviation	Definition
min	Minute or minimum
mL	Milliliter
mmHg	millimeter of mercury
MSDS	Material safety data sheet
ng	Nanogram
NOAEL	No observed adverse effect level
NQ	Nonquantifiable
PA	Protein adjusted
CCI [redacted]	
PLWH	People living with HIV
PK	Pharmacokinetic
POC	Proof of concept
POCBP	Participant of childbearing potential
POP PK	Population pharmacokinetics
PrEP	Pre-exposure prophylaxis
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	Corrected QT interval
QTcF	QT Interval corrected for heart rate according to Fridericia's formula
QTLs	Quality tolerance limits
RBCs	Red blood cells
RNA	Ribonucleic acid
RHF	Right-sided heart failure
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOC	Standard of care
SRT	Safety review team
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	Apparent terminal elimination phase half-life
t_{max}	Time to Cmax
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
UK	United Kingdom
US	United States
VH	ViiV Healthcare
VLD	Viral load decline
VSLC	ViiV safety and labelling committee
WBC	White blood cells

Abbreviation	Definition
WT	Wild type

TRADEMARK INFORMATION

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Phase 2a Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Orally Administered Investigational Capsid Inhibitors in HIV-1 Infected Treatment-Naïve Adults

Brief Title:

Proof of concept treatment study of orally administered VH4004280 or VH4011499 in HIV-1 infected adults

Rationale: (Refer to Section 2.1)

VH4004280 and VH4011499 (also referred to as GSK4004280 and GSK4011499, respectively) are investigational CAI in early clinical development. They belong to a novel class of antiretroviral (ARV) agents targeting CCI [redacted]. Study 218307 is a proof of concept (POC), randomized double blind, placebo-controlled Phase 2a study to characterize the antiviral activity, safety/tolerability, PK, and the relationship between PK and antiviral activity of VH4004280 and VH4011499 monotherapy administered orally over 10 days, in HIV-1 infected treatment-naïve adults. This study is being conducted following the availability of preliminary safety and PK clinical data from oral administration of these CAIs to healthy volunteers [TMF-15100069; TMF-14909676].

The purpose of this study is to evaluate the short-term safety and effect on reducing HIV-1 RNA levels from baseline for each orally administered CAI. Two different doses of each CAI will be evaluated in Part 1 of the study and have been chosen based on modelling of prior data from CCI [redacted] and prior pharmacokinetic data from the two ongoing Phase 1 healthy volunteer studies with orally dosed VH4004280 and VH4011499 (Studies 217058 and 218490, respectively). A third pre-specified dose of one or both CAIs may be evaluated in Part 2 of the study and will be informed by an interim analysis of Part 1.

The Phase 1 PK data support a CCI [redacted] for VH4004280 and VH4011499, respectively, during the short monotherapy treatment period designed in this study. The chosen doses are intended to target exposures that are efficacious (short-term antiviral effect) and are well tolerated. On Day 11, after the last HIV-1 RNA collection, study participants will switch to open-label combination ART (cART) prescribed by the investigator and sourced as per local guidelines. Participants will continue in the study and be monitored through Day 39.

This study will facilitate an initial understanding of the antiviral activity and safety profile of both CAIs in an HIV positive ARV naïve 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 two ongoing Phase 1 studies with CCI [redacted] and the single planned Phase 1 study with CCI [redacted], will inform subsequent clinical trials and Phase 2b clinical development.

Objectives, Endpoints, and Estimands: (Refer to Section 3)

Objectives	Endpoints
Primary	
To evaluate the antiviral activity of orally administered VH4004280 and VH4011499 monotherapy over 10 days in HIV-1 infected Treatment-Naïve (TN) participants	Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 11.
Secondary	
To assess the safety and tolerability of orally administered VH4004280 and VH4011499	• Incidence of adverse events (AEs), severity of AEs and AEs leading to study treatment discontinuation • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters (consisting of total and direct bilirubin, ALT, ALP and AST)
To characterize the pharmacokinetic profiles of orally administered VH4004280 and VH4011499	PK measures that include but are not limited to: • Maximum observed plasma drug concentration (Cmax), • Time to maximum observed plasma drug concentration (tmax), • Concentrations on Day 11 for VH4004280 and VH4011499.
To determine the relationship between the exposure levels of orally administered VH4004280 and VH4011499 and change in plasma HIV-1 RNA	VH4004280 and VH4011499 PK parameters with maximum change in plasma HIV-1 RNA from baseline through Day 11

Overall Design: (Refer to Section 4.1)

This is a Phase 2a, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled (by each capsid inhibitor), proof of concept clinical study to evaluate the antiviral effect, safety, tolerability and PK/pharmacodynamics (PD) of orally administered VH4004280 and VH4011499 monotherapy over 10 days in ART naive HIV-1 viremic adults.

Up to 42 treatment naïve participants with confirmed HIV-1 RNA ≥ 3,000 copies/mL and CD4 T-cell count ≥200 cells/μL will be recruited into this 2-part adaptive study. As per the study design schematic in Section 1.2, the first 14 participants screened and who are

found to meet all eligibility criteria will be randomly assigned on Day 1 to one of three placebo-controlled VH4004280 treatment groups (Part 1a: 6 active: 6 active: 2 placebo), followed by the next 14 participants randomly assigned on Day 1 to one of three placebo-controlled VH4011499 treatment groups (Part 1b: 6 active: 6 active: 2 placebo). Each CAI will be evaluated as double-blind monotherapy for 10 days (primary endpoint). On Day 11, after the collection of the HIV-1 RNA sample, participants will start open-label standard-of-care combination antiretroviral therapy that is selected by the investigator and locally sourced. CCI [redacted].

As described in Section 9.2, an informal interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1a have completed their Day 11 visit. A second informal interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1b have completed their Day 11 visit. The conduct of Part 2 is dependent on the results from Part 1 but if conducted, will evaluate a double-blind placebo controlled third pre-specified dose of one or both CAIs in up to an additional 14 participants [(Part 2a: 6 active VH4004280:1 placebo) and/or (Part 2b: 6 active VH4011499:1 placebo)].

Total duration of study participation is approximately 45 to 66 days based on the following: 7 to 14 days, with a maximum of 28 days permitted in some cases for screening/qualification period, 10 days for treatment with the study intervention and assessment at all planned visits and 28 days for follow up visits including the final follow up visit. See Section 1.3 (Schedule of Assessments) for additional details of activities during screening, the monotherapy period and the standard of care period.

Number of Participants: (Refer to Section 9.6)

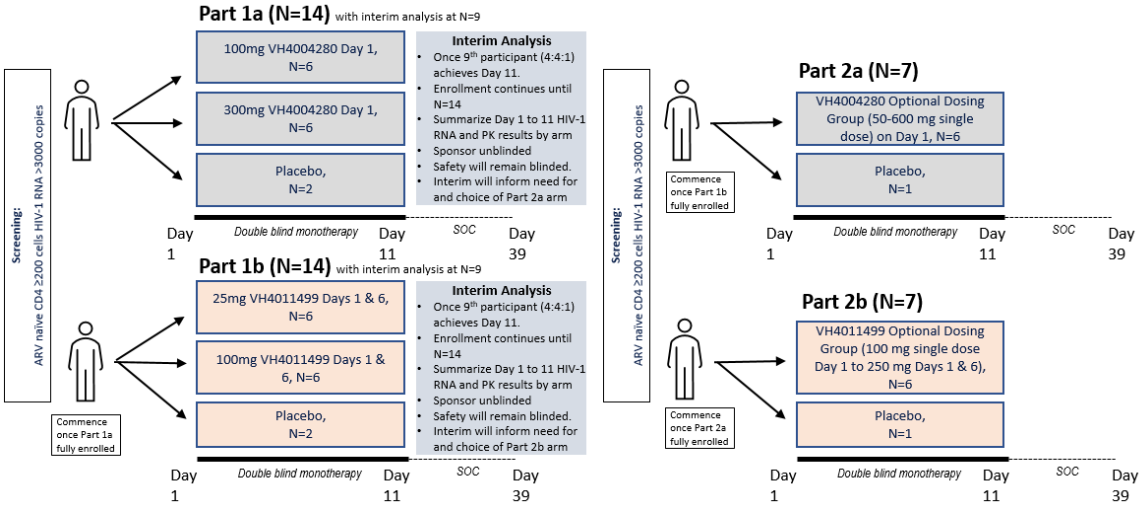
The sample size is based on feasibility and no formal calculation of power or sample size has been performed.

Data and Safety Monitoring/Other Committee: (Refer to Section 10.1.6)

A safety review team (SRT) is in place for each VH 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 studies of both CAIs.

In addition to the investigator's management of their participant's safety, participant safety will be routinely monitored by the VH medical monitor and the GSK safety leads. Pertinent findings and conclusions are shared with the VH/GSK product SRT for periodic review of the overall benefit risk profile of the product and escalated, as needed for governance to ViiV's Safety and Labelling Committee (VSLC).

1.2. Study design schematic



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.

Table 1 Schedule of activities - screening and monotherapy period

Clinical Procedures	Screening[1]	Monotherapy Treatment Period, Capsid Inhibitor (Double Blind) Day 1→Day 10					
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
	Approximately 7 to 14 days before Day 1	**Day 1** Fixed visit. No window.	**Day 2** Fixed visit. No window.	**Day 3, 4 or 5** Conduct visit on Day 3, 4 or 5	**Day 6** Fixed visit. No window.	**Day 7** Fixed visit. No window.	**Day 8, 9 or 10** Conduct visit on Day 8, 9 or 10
Outpatient clinic visit[2]	X	X	X	X	X	X	X
Informed consent	X						
Demography	X						
Inclusion / exclusion criteria	X	X					
Medical history, CDC classification	X	X					
Prior anti-retroviral therapy	X	X					
HIV-1 RNA	X	X	X	X	X	X	X
HIV-1 capsid genotype/phenotype		X	X	X	X	X	X
Lymphocyte T-cell subsets (CD4, CD8)	X	X					
Hepatitis B and C serologies	X						
SARS CoV-2 point of care test		X					
Physical exam[3]	X	X			X		
Height, weight, BMI	X						
Vital signs	X	X	X	X	X	X	X
C-SSRS administration (*Baseline* form)	X		X		X		
12-lead ECG	X	X	X				X
Safety labs (hematology, chemistry, urinalysis)[4]	X	X	X	X	X	X	X
Serum pregnancy (urine also on Day 1) for POCBP	X	X					
Plasma PK sampling[5]		X	X	X	X	X	X

Clinical Procedures	Screening[1]	Monotherapy Treatment Period, Capsid Inhibitor (Double Blind) Day 1→Day 10					
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
	Approximately 7 to 14 days before Day 1	**Day 1** Fixed visit. No window.	**Day 2** Fixed visit. No window.	**Day 3, 4 or 5** Conduct visit on Day 3, 4 or 5	**Day 6** Fixed visit. No window.	**Day 7** Fixed visit. No window.	**Day 8, 9 or 10** Conduct visit on Day 8, 9 or 10
Plasma for storage[6]		X	X	X	X	X	X
Pharmacogenetics (PGx) sample collection (if consented)		X					
AE/SAE assessment[7]	X	X	X	X	X	X	X
HIV-associated conditions[7]	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X
Interactive web response system for central randomization		X					
VH4004280/placebo	CCI [redacted]						
VH4011499/placebo							

1. 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, the screening period may be extended up to 28 days to allow receipt of all screening results and/or to accommodate scheduling.
2. The study requires 12 clinic visits. The visit schedule for each participant will be pre-planned and weekend, work schedules and clinic hours will be appropriately considered. At least one weekend clinic visit is required from Day 1 to Day 11.
3. Complete Physical Exam performed at Screening and Day 39/Early Discontinuation. A symptom directed physical exam will be performed at all other noted visits. Any abnormalities to be recorded as AEs. SAEs are assessed from the time of consent. Non-serious AEs are assessed from the time of first dose.
4. See Section 10.2 for details of clinical laboratory tests. Total bile acids (TBA), coagulation panel, and lipid panel (total cholesterol, HDL, LDL and triglycerides) required at Days 1, 6, 11, 25, 39/Early Discontinuation. Other clinical chemistry, hematology and urinalysis done at every visit. Fasting bloodwork is required for the lipid panel. CCI [redacted].
5. CCI [redacted]. A single PK draw will be conducted at all other visits. Refer to Section 8.5 for the collection schedule, permitted collection windows and further details.
6. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits. These samples will be used when needed, such as when samples are lost or where quantity is insufficient for testing. In the event samples are not used by study completion, they will be utilized for additional research on antiretroviral resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing).
7. The assessment of HIV-associated conditions and AEs/SAEs is conducted throughout the study. SAEs are assessed from the time of consent. Non-serious AEs are assessed from the time of first dose.

CCI [redacted]

Table 2 Schedule of activities – follow-up period with open label standard of care and early discontinuation visit

Clinical Procedures	Follow-Up Phase					Early Discontinuation[6]
	Visit 8	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12[5]**	
	Day 11 Fixed visit. No window.	**Day 18** +/- 3 day window.	**Day 25** +/- 3 day window	**Day 32** +/- 3 day window	**Day 39** +/- 3 day window	
Outpatient clinic visit	X	X	X	X	X	X
HIV-1 RNA	X Primary endpoint timepoint	X	X	X	X	X
HIV-1 capsid genotype/phenotype	X	X	X	X	X	X
Lymphocyte T-cell subsets (CD4, CD8)	X				X	X
Physical exam[2]					X	X
Height, weight, BMI	X				X	X
Vital signs	X	X	X	X	X	X
C-SSRS administration (*Since Last Visit* form)	X				X	X
12-lead ECG	X	X	X	X	X	X
Safety labs (hematology, chemistry, urinalysis)[3]	X	X	X	X	X	X
Serum pregnancy	X	X	X	X	X	X
Plasma PK single sample	X	X	X	X	X	X
Plasma for storage	X	X	X	X	X	X
AE/SAE assessment	X	X	X	X	X	X
HIV-associated conditions	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
Standard of care cART[1]	X	X	X	X	X	X

1. Standard of care cART will be chosen by the investigator and first dose will be directly observed at the end of the Day 11 visit. Choice of cART will be informed by local treatment guidelines, accessibility and locally run genotypic/phenotypic results (if available).
2. Complete Physical Exam performed at Screening and Day 39/Early Discontinuation. A symptom directed physical exam will be performed at all other noted visits. Any abnormalities to be recorded as AEs.
3. See Section 10.2 for details of clinical laboratory tests. Fasting bloodwork for the lipid panel is required at Days 1, 6, 11, 25, 39/Early Discontinuation.

4. Plasma samples for storage will be collected at each visit, 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 and consent is obtained for further research, then the stored samples may be utilized for additional research on antiretroviral resistance and/or HIV-1 disease biology/host immune response (excluding any human genetic testing).
5. Additional follow-up visits/contacts beyond Day 39 are permitted if a participant experiences a safety event that requires follow-up monitoring.
6. Early discontinuation assessments to be performed if a participant withdraws early from study.

2. INTRODUCTION

2.1. Study rationale

VH4004280 and VH4011499 (also referred to as GSK4004280 and GSK4011499, respectively) are investigational CAIs in early clinical development. They belong to a novel class of ARV agents targeting CCI [redacted]. Study 218307 is a POC, randomized double blind, placebo-controlled Phase 2a study to characterize the antiviral activity, safety/tolerability, PK, and the relationship between PK and antiviral activity of VH4004280 and VH4011499 administered orally over 10 days, in HIV-1 infected treatment-naïve adults. This study is being conducted following the availability of preliminary safety and PK clinical data from oral administration of these CAIs to healthy volunteers [TMF-15100069; TMF-14909676].

The purpose of this study is to evaluate the short-term safety and effect on reducing HIV-1 RNA levels from baseline for each orally administered CAI. Two different doses of each CAI will be evaluated in Part 1 of the study and have been chosen based on CCI [redacted] and prior pharmacokinetic data from the two ongoing Phase 1 healthy volunteer studies with orally dosed VH4004280 and VH4011499 (Studies 217058 and 218490, respectively). A third pre-specified dose of one or both CAIs may be evaluated in Part 2 of the study and be informed by interim results from Part 1.

The Phase 1 PK data support a CCI [redacted] for VH4004280 and VH4011499, respectively, during the short monotherapy treatment period designed in this study. The chosen doses are intended to target exposures that are efficacious (short-term antiviral effect) and are well tolerated. On Day 11, after the last HIV-1 RNA collection, study participants will switch to open-label combination ART (cART) prescribed by the investigator and sourced as per local guidelines. Participants will continue in the study and be monitored through Day 39.

This study will facilitate an initial understanding of the antiviral activity and safety profile of both CAIs in an HIV positive ARV naïve 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 two ongoing Phase 1 studies with CCI [redacted] and the single planned Phase 1 study with CCI [redacted], will inform subsequent clinical trials and Phase 2b clinical development

2.2. Background

2.2.1. Unmet Medical Need

It is estimated that approximately 38 million people are currently living with HIV/AIDS globally. This worldwide epidemic continues to grow at a rate of 1.5 million new infections and causes 0.7 million deaths per year [UNAIDS, 2021]. The current paradigm in the treatment of HIV-1 involves life-long therapy with multiple ARVs. While HIV-1

medicines are effective, there is a need for developing more conveniently dosed and more conveniently dosed ARV regimens.

CCI [redacted]

2.2.2. HIV-1 Capsid Inhibitors

ViiV has two investigational CAIs (VH4004280 and VH4011499) in early clinical development and which are CCI [redacted] could provide comparable efficacy to currently available daily dosed regimens, be generally safe and well-tolerated, CCI [redacted]

VH4004280 and VH4011499 belong to a novel class of ARV agents targeting a highly conserved region of the HIV-1 capsid protein. In-vitro experiments CCI [redacted]

In cell culture, both compounds exhibited potent antiviral activity against a wide spectrum of HIV-1 isolates and subtypes and demonstrated no cross-resistance with different ARV classes. No major safety signals have been identified from the nonclinical toxicology studies. The drug-drug interaction potential of VH4004280 and VH4011499 have been assessed in a series of in vitro studies. Based on the preliminary clinical drug-drug interaction (DDI) analysis, both VH4004280 and VH4011499 had no effect on the CCI [redacted] and thus both VH4004280 and VH4011499 CCI [redacted]. However, the clinical risk of potential drug-drug interactions with VH4004280 and VH4011499 as victims is currently unknown. The potential to develop these compounds as long-acting medicines is further supported by the emerging preliminary safety and tolerability data and

favorable pharmacokinetic profile from the ongoing healthy volunteer Phase 1 clinical studies evaluating VH4004280 and VH4011499.

2.2.3. Clinical Studies with Orally Administered VH4004280 and VH4011499

The safety and pharmacokinetic profiles of orally administered VH4004280 and VH4011499 are being characterized in healthy volunteers in ongoing Studies 217058 and 218490, respectively. Preliminary safety and PK results following oral administration of both CAIs have revealed no clinically significant findings and favorable pharmacokinetic profiles that support evaluation of both CAIs in this study following oral administration.

2.2.3.1. Study 217058 - Oral FTIH VH4004280

Study 217058 is an ongoing double-blind (sponsor unblinded), randomized, placebo-controlled, single and multiple-ascending-dose Phase 1 and FTiH study to evaluate the safety, tolerability and pharmacokinetics of VH4004280, when CCI [redacted] in healthy adult participants. The study is also designed to evaluate the DDI potential of VH4004280 and evaluate the safety, tolerability and PK of a VH4004280 CCI [redacted] in comparison with existing data from VH4004280 CCI [redacted]

Based on preliminary results, 41 participants and 18 participants have been enrolled in the single and MAD parts of the VH4004280 study, respectively. The study is currently ongoing and remains blinded (3:1 active to placebo random assignment to treatment).

The pharmacokinetic profile of VH4004280 is being initially evaluated following single oral dose administration from CCI [redacted]. Based on the preliminary analysis, VH4004280 has a median CCI [redacted] in concentration and a mean CCI [redacted]. VH4004280 showed a CCI [redacted]. There was an approximately CCI [redacted] from Day 1 in Cmax and AUC0-tau, respectively following CCI [redacted] Based on the preliminary clinical DDI analysis, VH4004280 CCI [redacted] and thus VH4004280 CCI [redacted]

Overall, there have been no clinically significant safety findings, serious adverse events (SAEs), deaths, pregnancies, trends in vital signs, laboratory parameters, ECG parameters nor discontinuations due to adverse events (AEs). More detailed information can be found in the CIBs [RPS-CLIN-048482; RPS-CLIN-056826].

2.2.3.2. Study 218490 - CCI [redacted] FTIH VH4011499

Study 218490 is an ongoing double-blind (sponsor unblinded), randomized, placebo-controlled, single and multiple-ascending-dose Phase 1 and first time in human study to evaluate the safety, tolerability and pharmacokinetics of VH4011499, when administered

as a [redacted], in healthy adult participants. The study is also designed to evaluate the DDI potential of VH4011499 and evaluate the safety, tolerability and PK of a VH4011499 [redacted] in comparison with existing data from VH4011499 [redacted].

Based on preliminary results, 32 participants and 19 participants have been enrolled in the single and MAD parts of the VH4011499 study, respectively. The study is currently ongoing and remains blinded (3:1 active to placebo random assignment to treatment.

The pharmacokinetic profile of VH4011499 is being initially evaluated following single oral dose administration from 25 to 1875 mg [redacted]. Based on the preliminary analysis, VH4011499 has a median [redacted] and a mean [redacted]. VH4011499 showed a [redacted] in exposure from [redacted] There was an approximately [redacted] in Cmax and AUC0-tau, respectively following [redacted]. Based on the preliminary clinical DDI analysis, VH4011499 had no effect on the [redacted] and thus VH4011499 [redacted].

Overall, there have been no clinically significant safety findings, deaths, SAEs considered related to treatment, pregnancies, trends in vital signs, laboratory parameters, ECG parameters nor discontinuations due to AEs. More detailed information can be found in the CIB [RPS-CLIN-056829].

2.2.4. Further Non-clinical Data about VH4004280 and VH4011499

A detailed description of the non-clinical pharmacology, pharmacokinetics, toxicology, virology, and chemistry and manufacturing of VH4004280 and VH4011499 is provided in the respective CIBs [RPS-CLIN-048482; RPS-CLIN-026329; RPS-CLIN-047476; RPS-CLIN-046304; RPS-CLIN-056829; RPS-CLIN-056826].

[redacted]

CCI [redacted]

2.3. Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VH4004280 and VH4011499 may be found in their respective CIBs [RPS-CLIN-048482; RPS-CLIN-026329; RPS-CLIN-047476; RPS-CLIN-046304; RPS-CLIN-056829; RPS-CLIN-056826].

In the ongoing Phase 1 oral studies in healthy volunteers with VH4004280 and VH4011499 (both blinded), no untoward safety signals have been identified from either the single ascending or multiple dose parts of the studies. In both studies, there have been no deaths, no trends in vital signs, laboratory or ECG parameters and no discontinuations due to AEs. There have been no SAEs in the VH4004280 study, and in the VH4011499 study, there was one SAE (seriousness criteria: hospitalization) of Grade 2 chest pain, which occurred on Day 27 following a single dose of CCI [redacted]; results of ECG and cardiac enzyme tests were negative, and the event was considered by the investigator to be related to methamphetamine and unrelated to study treatment.

The toxicity of VH4004280 and VH4011499 has been evaluated in CCI [redacted] studies of up to 4 weeks duration in rats and dogs, and CCI [redacted] studies of up to 13 weeks duration using the CCI [redacted] of VH4004280 and VH4011499 in both rats and dogs. In the CCI [redacted] studies with both compounds, there were no adverse findings in either rat or dog at all doses tested.

In the 13-week CCI [redacted] study in dogs with VH4004280 using the CCI [redacted], there were no adverse findings up to the highest dose tested CCI [redacted]. In the 13-week CCI [redacted] study in rats, the highest dose tested CCI [redacted] was not considered tolerated due to clinical signs of suspected dehydration, along with lower body weights. The intermediate dose tested CCI [redacted] was the NOAEL for VH4004280.

In the 13 week CCI [redacted] studies with VH4011499 using the CCI [redacted], the NOAELs were considered to be greater than or equal to the highest CCI [redacted] doses tested in rats CCI [redacted] and dogs CCI [redacted] and the highest/only CCI [redacted] doses tested in rats CCI [redacted] and dogs CCI [redacted] as there were no adverse findings in either species via either route. There were decreases in body weight and/or food consumption following days of dosing in both species, but none were considered adverse as these were transient.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug VH4004280 and/or VH4011499		
Drug-induced liver injury (and/or clinically significant liver chemistry elevations for **VH4011499** only)	**Nonclinical** In vitro, both VH4004280 and VH4011499 inhibited CCI with IC50 values of CCI respectively, and the CCI) with IC50 values of CCI respectively. CCI can cause CCI can cause accumulation of CCI which may lead to CCI . **VH4004280**: In the definitive 28-day CCI repeat dose dog study with VH4004280, minimally increased mean liver weights and increased total bile acids (1 animal) were seen at CCI , however these were not associated with any microscopic liver findings. At the same dose, there were increases in fibrinogen concentrations in males (1.56X control) and females (1.55X control), and prolongation of activated partial thromboplastin time in females (1.87X control). In the 28-day repeat dose rat study with VH4004280, there were no weight changes and no microscopic findings in the liver. Additionally, there were no bilirubin changes in these studies. Whilst these changes could reflect possible hepatocellular and/or hepatobiliary injury, they were of low magnitude and without correlating histopathological findings. In the definitive 13-week VH4004280 CCI rat study, treatment related minimal to mild hepatocellular vacuolation was	Participants with current or history of liver disease, with coinfection with HBV or HCV or known hepatic or biliary abnormalities are excluded from participation in this study (refer to Section 5.2). Participants will be closely monitored for liver related AE and laboratory abnormalities, including serum total bile acids and coagulation parameters. Liver chemistry participant stopping criteria are defined (refer to Section 7.1.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	observed in the highest dose group CCI [redacted]. This finding, not considered adverse, consisted of macro and microvesicles in the cytoplasm of centrilobular hepatocytes and correlated to pale discoloration of the liver in two males. Although a statistically significant increase in the mean relative (to body) liver weight occurred in males at this dose, this was largely considered related to body weight decrements. In addition, there were increases in total bilirubin (up to 2.38X control) and total bile acids (up to 2.90X control) at CCI [redacted] on Days 28 and 85. There were no treatment-related changes in coagulation parameters in this study. There were no liver-related findings in the definitive 3-month VH4004280 CCI [redacted] dog study and no changes in coagulation parameters. **VH4011499:** In the definitive 13-week VH4011499 CCI [redacted] studies in rats and dogs, there were no adverse findings in the liver, including no increases in liver enzymes, total bile acids, bilirubin or coagulation parameters. In the definitive 28-day repeat dose CCI dog study with VH4011499, at the highest dose/NOAEL CCI [redacted], there were increases relative to pre-dose in alanine and aspartate aminotransferases (ALT increased by up to 11.3 fold in 4/6 dogs, AST increased by up to 3.0 fold in 2/6 dogs) and glutamate dehydrogenase (GLDH increased by up to 6.2 fold in 4/6 dogs) with no histologic correlates in the liver and no changes in liver weight. No increases in bilirubin were observed. In the definitive 28-day repeat dose study in the rat (highest dose/NOAEL CCI [redacted] there were no adverse effects of VH4011499,	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	including no increases in liver enzymes, total bile acids, bilirubin or coagulation parameters. **Clinical (blinded data)**: No trends in liver or coagulation parameters have been observed in the ongoing Phase 1 oral clinical studies with VH4004280 or VH4011499.	
Increases in cholesterol and triglycerides	**Nonclinical** **VH4004280:** In the definitive 28-day CCI repeat dose toxicity studies with VH4004280, increases in mean serum total cholesterol concentration were observed in rats and dogs at the highest doses tested (CCI [redacted]. Increased triglycerides were also noted in dogs at CCI [redacted] In both species, there were no macroscopic or microscopic changes in the liver at any dose level. In the definitive 3-month VH4004280 CCI [redacted] rat study, increases in total cholesterol concentrations (up to 1.70X control) at CCI [redacted] on Days 28 and 85 were observed. There were no increases in lipids in the definitive 3-month VH4004280 CCI [redacted] dog study. **VH4011499**: No increases in cholesterol or triglycerides were observed in the definitive 28-day CCI or 13-week CCI [redacted] toxicity studies in dog and rat with VH4011499. **Clinical (blinded data):**	Participants will be closely monitored for relevant AEs and laboratory abnormalities. Lipid panel is included in routine clinical laboratory tests as detailed in the SoA (Section 1.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No trends in lipid parameters have been observed in the ongoing Phase 1 oral clinical studies with VH4004280 or VH4011499.	
Hematology changes	**Nonclinical** **VH4004280:** In the 28-day CCI dose dog study CCI CCI increases in neutrophils and monocyte counts were observed. In the definitive 13-week VH4004280 CCI rat study, treatment-related hematologic changes were observed at CCI, and included increases in lymphocyte, neutrophil and/or white blood cell counts, decreases in hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, increases in red blood cell counts, red cell distribution width concentration and/or in reticulocyte counts. There were no changes in hematology parameters in the definitive 13-week VH4004280 CCI dog study. **VH4011499:** No changes in hematology parameters were observed in the definitive 28 day CCI or 13-week CCI toxicity studies in dog and rat with VH4011499. **Clinical (blinded data):** No trends in hematology parameters have been observed in the ongoing Phase 1 oral clinical studies with VH4004280 or VH4011499.	Participants will be closely monitored for relevant AEs and laboratory abnormalities. Hematology Panel is included in routine clinical laboratory tests as detailed in the SoA (Section 1.3). See Section 8.3.7 for clinical stopping criteria applicable to this potential risk.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Acute pulmonary injury (**VH4004280** only)	**Nonclinical** In a single dose dose-range finding dog study with VH4004280 CCI [redacted], inflammatory changes were noted on lung histology. At CCI [redacted] histological findings in the lungs of 3/3 dogs included interstitial expansion containing primarily mononuclear cells and fibrin and multifocal mixed cell bronchioalveolar inflammation with alveolar infiltrates comprising vacuolated macrophages, neutrophils and few, non-vacuolated, mononuclear cells. In some regions, there was damage to the alveolar wall, evidenced by the presence of fibrin (free and phagocytized), hemorrhage and pneumocytes ranging from flattened to larger and vacuolated. These microscopic lung findings correlated to gross changes observed in the lung margins. At CCI [redacted], there were no gross observations at necropsy and histologic changes in the lung consisted of minimal bronchioalveolar mixed cell inflammation in 2/3 dogs. There were no microscopic findings in 3/3 dogs given CCI [redacted] There were no histological findings in the lung in the 28-day definitive rat and dog repeat dose studies (CCI [redacted]) conducted with the VH4004280 CCI formulation being used in Study 217058. There were no histological findings in the lung in the VH4004280 definitive CCI 13-week CCI [redacted] in both rat (up to doses of CCI [redacted] and dog CCI [redacted]	Participants with current or history of respiratory disease are excluded from participation in this study (refer to Section 5.2). Participants will receive VH4004280 by the CCI [redacted] and lower than those observed in CCI 28-day toxicity studies in both rat and dog, where there were no histologic findings in the lungs. Participants will be closely monitored for relevant AEs, vital signs and laboratory abnormalities.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No similar findings have been observed in nonclinical studies with VH4011499.	
Effects on embryo-fetal development	**Nonclinical** **VH4004280**: Rats and rabbits were given daily CCI doses of VH4004280 in embryo-fetal development studies. There were no effects on embryo-fetal development parameters or maternal toxicity in rats at up to CCI In rabbits, maternal toxicity (body weight losses and reductions in body weight gains) occurred at doses CCI in the absence of any effects on food consumption or clinical signs. At CCI maternal toxicity resulted in decreased fetal weights and skeletal variations (unossified sternebrae) but no malformations. Similar findings did not occur at lower doses, and these findings are related to maternal toxicity and not direct effects on embryo-fetal development. **VH4011499:** In embryo-fetal development studies, rats were given daily CCI doses and rabbits were given CCI of VH4011499.There were no effects on embryo-fetal development parameters or maternal toxicity in rats at up to CCI In rabbits, maternal toxicity (reduced body weight gains and food consumption) was noted at CCI with no effects on embryo-fetal development parameters at doses up to CCI	Participants of childbearing potential (POCBP) must be using acceptable forms of birth control through to Day 39. POCBP will have pregnancy testing conducted prior to study intervention and during the study. 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI [redacted]		CCI [redacted] should be dosed with caution if co-administered with VH4004280 from Day 1 through Day 11.
		CCI [redacted] should be dosed with caution if co-administered with VH4011499 or VH4004280 from Day 1 through Day 11. CCI [redacted] with CCI [redacted] are not permitted from Day 1 through Day 11).
Other (both VH4004280 and VH4011499)		
Emergence of resistance	CCI [redacted]	Short monotherapy period (10 days) followed immediately at the end of the Day 11 visit by initiation of cART. The dose and dose regimens selected are intended to rapidly achieve plasma concentrations that provide therapeutic benefit. The lowest starting dose that is pre-specified aims to target CCI [redacted] is unlikely to occur under these conditions.

2.3.2. Benefit assessment

This study in treatment naïve, HIV-1 infected but otherwise healthy participants is a short-term monotherapy design. There is no expected longer-term anti-HIV benefit to administration of VH4004280 or VH4011499 in this study. The monotherapy phase is 10 days with frequent outpatient visits and a 4 week follow up period during which participants will continue to be closely monitored. On Day 11, after the collection of the HIV-1 RNA sample, participants will start open-label standard-of-care combination antiretroviral therapy that is selected by the investigator.

2.3.3. Overall benefit-risk conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with VH4004280 and VH4011499 are justified by the anticipated benefits that may be afforded to people living with HIV-1 infection.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objectives	Endpoints
Primary	
To evaluate the antiviral activity of orally administered VH4004280 and VH4011499 monotherapy over 10 days in HIV-1 infected Treatment-Naïve (TN) participants	Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 11.
Secondary	
To assess the safety and tolerability of orally administered VH4004280 and VH4011499	• Incidence of adverse events (AEs), severity of AEs and AEs leading to study treatment discontinuation • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters (consisting of total and direct bilirubin, ALT, ALP and AST)
To characterize the pharmacokinetic profiles of orally administered VH4004280 and VH4011499	PK measures that include but are not limited to: • Maximum observed plasma drug concentration (Cmax), • Time to maximum observed plasma drug concentration (tmax), • Concentrations on Day 11 for VH4004280 and VH4011499
To determine the relationship between the exposure levels of orally administered VH4004280 and VH4011499 and change in plasma HIV-1 RNA	VH4004280 and VH4011499 PK parameters with maximum change in plasma HIV-1 RNA from baseline through Day 11

CCI

[redacted]

Endpoints	Estimand			
	Population	**Treatment**	**Summary Measure**	**Intercurrent event (IE) / strategy / rationale**
Primary Objective: To evaluate the antiviral activity of orally administered VH4004280 and VH4011499 monotherapy over 10 days in HIV-1 infected Treatment-Naïve (TN) participants				
• Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 11.	Overtly healthy (other than HIV-1 infection) treatment naïve individuals	VH4004280 or placebo single dose on Day 1 or VH4011499 or placebo single dose on Day 1 and Day 6	Mean of maximum change from Baseline in log10 HIV-1 RNA during Days 1-11	Discontinuation of study treatment due to any reason: **Treatment policy strategy,** i.e., any HIV-1 RNA data available after study treatment discontinuation day + 1 and prior to starting SOC will be used in calculation of max VLD Use of SOC medication prior to Day 11: **While on-treatment strategy**, i.e., HIV-1 RNA collected after initiation of SoC, if for any reason this takes place prior to Day 11 will be excluded from calculation of max VLD Use of prohibited medication: **Treatment policy strategy**, i.e., any HIV-1 RNA data available after use of prohibited medication will be used in calculation of max VLD Missed or partial doses of study treatment: **Treatment policy strategy,** i.e., HIV-1 RNA collected after missed or partial dose(s) will be used in calculation of max VLD *Rationale:* Interest is in evaluating efficacy irrespective of study treatment discontinuation or missed/partial doses, or use of prohibited medications, hence a treatment policy strategy is appropriate. Also, interest is to evaluate efficacy of VH4004280/VH4011499 monotherapy and not in combination with other antiretroviral medication hence a while on-treatment strategy is appropriate. *Note: discontinuation or missed or partial doses of VH4004280 is not possible as only a single dose on Day 1 is administered, hence these IEs apply only to VH4011499 and to placebo matched for VH4011499.*
Secondary Objective: To assess the safety and tolerability of orally administered VH4004280 and VH4011499				

Endpoints	Estimand			
	Population	**Treatment**	**Summary Measure**	**Intercurrent event (IE) / strategy / rationale**
• Incidence of adverse events (AEs), severity of AEs and AEs leading to study treatment discontinuation • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters	Overtly healthy (other than HIV-1 infection) treatment naïve individuals	VH4004280 or placebo CCI [redacted] or VH4011499 or placebo CCI [redacted]	• 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 ○ Summaries (mean, median, std, Q1, Q2, min, max) of change from baseline in liver	Discontinuation of study treatment: **Treatment policy strategy,** i.e., all data to be used regardless of whether the study treatment discontinuation has occurred Use of SOC medication prior to Day 11: **While on-treatment strategy**, i.e., Safety data collected after initiation of SoC, if for any reason this takes place prior to Day 11 will be excluded from monotherapy Safety summaries Use of prohibited medication: **Treatment policy strategy,** i.e., all data to be used regardless of whether prohibited medication has been used *Rationale:* There is interest in evaluating and reporting monotherapy safety events from the monotherapy period and regardless of whether participants have completed monotherapy treatment or received prohibited medication *Note: discontinuation of VH4004280 treatment is not possible as only a single dose on Day 1 is administered, hence this IE applies only to VH4011499 and to placebo matched for VH4011499.*

Endpoints	Estimand			
	Population	**Treatment**	**Summary Measure**	**Intercurrent event (IE) / strategy / rationale**
			panel laboratory parameters ○ Number and percentage of participants with maximum grade toxicity relative to Baseline	
Secondary Objective: To characterize the pharmacokinetic profiles of orally administered VH4004280 and VH4011499				
Concentration on Day 11 and PK parameters including ○ Cmax ○ tmax	Overtly healthy (other than HIV-1 infection) treatment naïve individuals	VH4004280 or placebo CCI [redacted] or VH4011499 or placebo CCI [redacted]	Summary statistics (e.g., arithmetic mean, median, std, minimum, maximum, geometric mean, sd (log), %CVb)	Discontinuation of monotherapy treatment with VH4011499: **While on-treatment strategy,** i.e., concentration values after study treatment discontinuation day + 1 will be excluded from analysis Use of prohibited medication: **treatment policy strategy**, i.e., all PK data to be used regardless of whether prohibited medication was used *Rationale:* Discontinuation of VH4011499 treatment may bias the evaluation of Pharmacokinetic behavior of VH4011499 as expected during and after the end of 10 days monotherapy period *Note: discontinuation of VH4004280 treatment is not possible as only a single dose on Day 1 is administered*

4. STUDY DESIGN

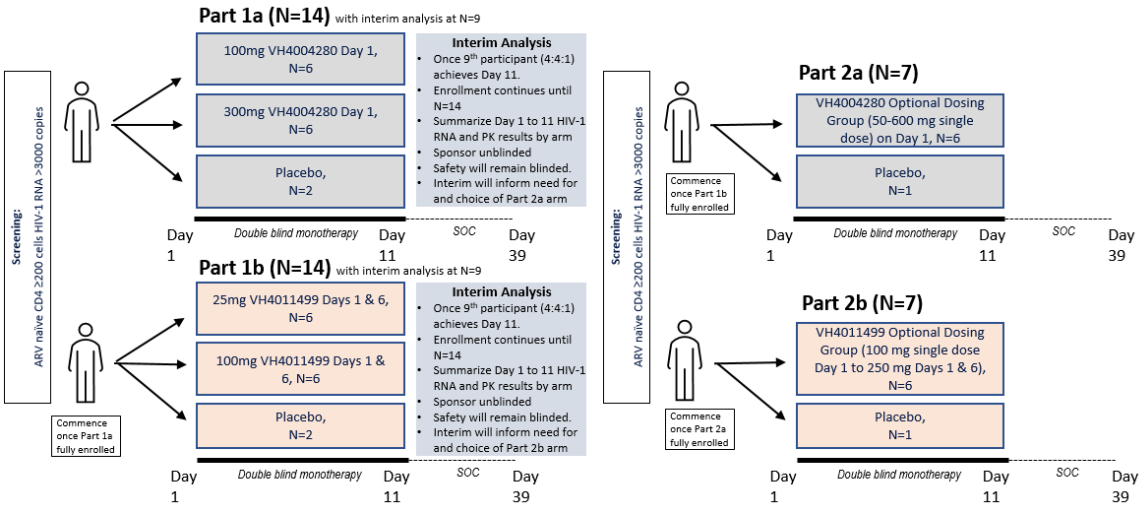
4.1. Overall design

This is a Phase 2a, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled (by each CAI), proof of concept clinical study to evaluate the antiviral effect, safety, tolerability, and PK/pharmacodynamics (PD) of CCI [redacted] HIV-1 viremic adults.

Up to 42 treatment naïve participants with confirmed HIV-1 RNA ≥ 3,000 copies/mL and CD4 T-cell count ≥200 cells/µL will be recruited into this 2-part adaptive study. As per Figure 1, the first 14 participants screened and who are found to meet all eligibility criteria will be randomly assigned on Day 1 to one of three placebo-controlled VH4004280 treatment groups (Part 1a: 6 active: 6 active: 2 placebo), followed by the next 14 participants randomly assigned on Day 1 to one of three placebo-controlled VH4011499 treatment groups (Part 1b: 6 active: 6 active: 2 placebo). Each CAI will be evaluated as double-blind monotherapy for 10 days (primary endpoint). On Day 11, after the collection of the HIV-1 RNA sample, participants will start open-label standard-of-care combination antiretroviral therapy that is selected by the investigator and locally sourced. Participants will be followed weekly through Day 39 to ensure that CAI drug concentrations have declined to BLQ.

As described in 9.2, an informal interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1a have completed their Day 11 visit. A second informal interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1b have completed their Day 11 visit. The conduct of Part 2 is dependent on the results from Part 1 but if conducted, will evaluate a double-blind placebo controlled third pre-specified dose of one or both CAIs in up to an additional 14 participants [(Part 2a: 6 active VH4004280:1 placebo) and/or (Part 2b: 6 active VH4011499:1 placebo)].

Figure 1 Study design schematic



Total duration of study participation is approximately 45 to 66 days based on the following: 7 to 14 days, with a maximum of 28 days permitted in some cases for screening/qualification period, 10 days for treatment with the study intervention and assessment at all planned visits and 28 days for follow up visits including the final follow up visit. See Section 1.3 (Schedule of Assessments) for additional details of activities during screening, the monotherapy period and the standard of care period. This study includes the option of an additional 12 weeks post study VH/GSK reimbursement of locally sourced cART standard of care, as applicable.

4.2. Scientific rationale for study design

This is a Phase 2a, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled, proof of concept clinical study to evaluate the antiviral effect, safety, tolerability, and PK/pharmacodynamics (PD) of orally administered VH4004280 and VH4011499 monotherapy over 10 days in approximately 42 ART naive HIV-1 viremic adults.

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 each orally administered CAI. This study will facilitate an initial understanding of the antiviral activity and safety profile of both CAIs in an HIV positive ARV naïve 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 two ongoing Phase 1 studies with CCI [redacted] and the single planned Phase 1 study with CCI [redacted], will inform subsequent clinical trials and Phase 2b clinical development.

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 of each CAI 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 each CAI and placebo.

The two-part adaptive design will allow for interim evaluation of the exposure-antiviral response data to determine if evaluation of a third dose of one or both CAIs would be informative to properly characterize the exposure-antiviral relationship. If a third dose is not needed, then exposing additional participants to the investigational CAI can be avoided.

4.2.1. Participant input into design

Participants living with HIV-1 were not engaged in development of this short-term monotherapy proof-of-concept study design.

4.3. Justification for dose

The VH4004280 and VH4011499 doses for investigation in this study are defined by emerging PK and safety data from the ongoing oral Phase 1 studies, preclinical potency data [RPS-CLIN-048482; RPS-CLIN-026329; RPS-CLIN-047476; RPS-CLIN-046304; RPS-CLIN-056829; RPS-CLIN-056826; TMF-14580566; TMF-14086139; TMF-14580566], and CCI [redacted]

A therapeutic dose for VH4004280 and VH4011499 is proposed where majority of participants maintain, concentrations CCI [redacted], that are expected to provide exposures that result in a near maximal change from baseline in plasma HIV-1 RNA by Day 11.

Thus, VH4004280 and VH4011499 doses in the current study aim to provide the following exposures through the 10-days monotherapy period:

- CCI [redacted] aimed to characterize the near maximal decline in HIV-1 RNA.
- CCI [redacted] aimed to characterize the near maximal decline in HIV-1 RNA.
- Based on the interim analysis of exposures and response, a dose corresponding to 10-days CCI [redacted] aimed to confirm the maximal decline in HIV-1 RNA.

A population pharmacokinetic (POP PK) analysis was conducted using preliminary data from the ongoing oral Phase 1 studies for VH4004280 and VH4011499 [TMF-15100069; TMF-14909676]. Based on the POP PK analysis, CCI [redacted] Similarly, using a POP PK analysis for VH4011499, CCI [redacted]

Thus, VH4004280 doses for the current study are expected to be CCI [redacted] for Part 1 and a dose between approximately CCI [redacted] will be selected for Part 2 based on interim analysis. Similarly, VH4011499 doses for the current study are expected

to be CCI [redacted] for Part 1 and a dose between approximately CCI [redacted] will be selected for Part 2 based on interim analysis. VH4004280 and VH4011499 doses in Part 2 may be adjusted based on preliminary analyses of exposure and response from Part 1.

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 39 End of Study (EOS) visit. The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

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

Up to 42 HIV-infected adults (treatment naive) 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.

5.1. Inclusion Criteria

Entry into screening nor meeting all eligibility criteria does not guarantee enrollment into the study. To manage the total study enrollment, VH/GSK at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

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

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

Type of Participant and Disease Characteristics
2. Participants who are overtly healthy (other than HIV-1 infection) as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Screening CD4+ T-cell count ≥200 cells/µL.

4. Documented HIV-1 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. Treatment-naïve: Defined as no ARVs (in combination or monotherapy) received after the diagnosis of HIV-1 infection. Prior use of oral PreP is permitted and meets inclusion. Prior use of parenteral PreP is exclusionary.

Weight

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

Sex and Contraceptive/Barrier Requirements

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

   Participants Male at birth: There are no contraceptive requirements for participants who were male at birth.

   Participants Female at birth: A participant who was female at birth is eligible to participate if they are not pregnant and not breastfeeding. Participant of childbearing potential (POCBP) must be using acceptable forms of birth control through to Day 39. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a POCBP with an early undetected pregnancy. Refer to Section 10.4 for more details.

Informed Consent

8. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and stated in this protocol.

Other Inclusions

9. Participant must be willing and able to start locally accessible and commercially available cART on Study Day 11. The investigator will choose the standard of care cART according to local treatment guidelines, accessibility and locally run genotypic/phenotypic results (if available).

5.2. Exclusion Criteria

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

MEDICAL CONDITIONS

1. Women who are breastfeeding or plan to become pregnant or breast feed during the study.
2. Participants with acute 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.
3. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy during the study. Refer to Section 10.8 for more details.
4. Untreated syphilis infection [positive rapid plasma reagin (RPR) at screen] without documentation of treatment. Participants who have successfully completed treatment at least 7 days prior to Day 1 are eligible if recruitment is open.
5. 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 VH medical monitor for inclusion of the participant prior to randomization.
6. 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.
7. 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; Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the investigator (with or without psychiatric evaluation), could interfere with the participant's ability to comply with the dosing schedule and protocol evaluations or which might compromise the safety of the participant.
8. Any history of significant underlying psychiatric disorder, in the opinion of the investigator or VH medical monitor, including but not limited to schizophrenia, bipolar disorder with or without psychotic symptoms, other psychotic disorders, or schizotypal (personality) disorder; or a clinical assessment of suicidality based on the responses on the C-SSRS.
9. Any history of major depressive disorder with or without suicidal features, or anxiety disorders, that required medical intervention (pharmacologic or not) such as hospitalization or other inpatient treatment and/or chronic (>6 months) outpatient treatment. Participants with other conditions such as adjustment disorder or dysthymia that have required shorter term medical therapy (<6 months) without inpatient treatment and are currently well-controlled clinically or resolved may be considered for entry after discussion and agreement with the VH medical monitor.

10. Any condition which, in the opinion of the investigator, may interfere with the absorption, distribution, metabolism or excretion of the study drugs or render the participant unable to take oral medication.
11. Current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).
12. A pre-existing condition, in the opinion of the investigator or VH medical monitor, that could interfere with normal gastrointestinal anatomy or motility (e.g., gastroesophageal reflux disease [GERD], gastric ulcers, gastritis, inflammatory bowel disease), hepatic and/or renal function, that could interfere with the absorption, metabolism, and/or excretion of the study interventions or render the participant unable to take oral study treatment.
13. 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 VH medical monitor, will interfere with the safety for the individual participant.
14. 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	
QTc interval (Fridericia's)	>450 msec	>470 msec

Note: [1]A heart rate from 100 to 110 beats per minute (bpm) can be rechecked by ECG or vitals within 30 minutes to verify eligibility. [2]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 used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the study.

15. To assess any potential impact on participant eligibility regarding safety, the investigator must refer to the CIBs 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.

PRIOR/CONCOMITANT THERAPY

CCI

[redacted]

17. History of sensitivity to any of the study medications, or their components or drugs of their class, or a history of drug or other allergy that, in the opinion of the investigator or VH medical monitor, contraindicates their participation.
18. Participants who require concomitant medications known to be associated with a prolonged QTc (see list from https://www.crediblemeds.org).
19. Treatment with any of the following agents within 28 days of Screening: radiation therapy, cytotoxic chemotherapeutic agents, any systemic immune suppressant.
20. Prior use of [redacted] for any reason is exclusionary.
21. Participants receiving any protocol-prohibited medication and who are unwilling or unable to switch to an alternate medication.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

22. The participant has received an investigational HIV vaccine (immunotherapeutic or immunomodulatory).
23. Exposure to an approved vaccine within 14 days prior to Day 1.
24. Exposure to an investigational drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of study intervention.

    Note: Receipt of a SARS-CoV-2 vaccine that has received emergency, conditional, or standard market authorization is allowed at least 14 days prior Day 1 if the investigator determines that the benefit-risk profile for that individual study participant is favorable. The use of other investigational SARS-CoV-2 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
25. Participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
26. Exposure to more than four new investigational drugs or vaccines within 12 months prior to Day 1.
27. 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.

DIAGNOSTIC ASSESSMENTS

28. Presence of Hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) at screening
    - Evidence of Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg).

- Participants who are negative for HBsAg should also be tested for Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (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.
- 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).

29. 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)

30. 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

31. Positive SARS-CoV-2 polymerase chain reaction test, having signs and symptoms which in the opinion of the investigator are suggestive of COVID-19 (i.e., fever, cough etc.) on Day 1, or having contact with known COVID-19 positive person/s in the 14 days prior to Day 1.
32. Creatinine clearance (eGFR) of < 50 mL/min/1.73 m2 via CKD-EPI method [Delgado, 2021].
33. Alanine aminotransferase (ALT) ≥1.5 x upper limit of normal (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.
34. Any Grade 3-4 laboratory abnormality at Screening, except for a Grade 4 creatine phosphokinase (CPK) and lipid abnormalities (e.g., total cholesterol, triglycerides, etc.) will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any lab abnormality is allowed within a single Screening period to determine eligibility.
35. Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
36. Any positive result for illicit drug use (e.g., cocaine, heroin) at Screening. A positive screen for marijuana/THC is not exclusionary. Refer to Section 5.3.2 for guidance to be given to the participant.

OTHER EXCLUSIONS
37. 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 white wine or 1.5 ounces (45 mL) of 80 proof distilled spirits. 38. Regular use of drugs of abuse

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, 6, 11, 25, and 39/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 CCI and dosing.

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 11 visit. Excessive consumption is defined as more than one glass of red wine or juice or one fruit per day, in combination.

5.3.2. Caffeine, alcohol, tobacco, marijuana/THC and illicit drug use

- During the study alcohol consumption will be limited to the following: An average weekly intake of <14 drinks for males or <7 drinks 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.
- No alcohol will be consumed for the intensive PK days (CCI [redacted] until after the final assessment of the day and release from the clinic.
- No caffeine or xanthine containing products (e.g., coffee, tea, cola drinks, and chocolate) will be consumed for the intensive PK days (CCI [redacted]

CCI [redacted] until after the final assessment of the day and release from the clinic.

- Only clinically minor to moderate use (as determined by the investigator) of tobacco or nicotine containing products will be allowed during study participation, with extremely limited use on the intensive PK days CCI [redacted] until after the final assessment of the day and release from the clinic.
- Any positive result for illicit drug use (e.g., cocaine, heroin) at Screening is exclusionary. A positive screen for marijuana / THC is not exclusionary. Participants should refrain from the use of marijuana from Day 1 through the Day 11 visit.

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 studies.

5.4. Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled (i.e., 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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number. Previously assigned participant numbers are to be recorded in the participants' eCRF.

5.5. Criteria for temporarily delaying enrollment/randomization

Refer to Section 7.1 for safety criteria that could temporarily pause further recruitment into the study.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in Table 3 and includes VH4004280/placebo CCI and VH4011499/placebo CCI. Study intervention does not include locally sourced open-label SOC that is first administered at the end of the Day 11 visit and after final collection of the primary endpoint data (Day 11 plasma HIV-1 RNA sample).

6.1. Study interventions administered

Table 3 Study interventions administered

Intervention Label	VH4004280 CCI	Matched placebo for VH4004280 CCI	VH4011499 CCI	Matched placebo for VH4011499 CCI
Intervention Name	VH4004280 CCI	Matched placebo for VH4004280 CCI	VH4011499 CCI	Matched placebo for VH4011499 CCI
Intervention Description	CCI			
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strengths	CCI			
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP and NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
CCI				
Current Alias	GSK4004280	Not applicable	GSK4011499	Not applicable

Table 4 VH4004280 study arms

Arm Title	VH4004280	VH4004280	Placebo for VH4004280	VH4004280	Placebo for VH4004280
Part	Part 1a	Part 1a	Part 1a	Part 2a	Part 2a

Arm Title	VH4004280	VH4004280	Placebo for VH4004280	VH4004280	Placebo for VH4004280
Arm Type	Experimental	Experimental	Placebo	Experimental	Placebo
Regimen	1	2	3	4	5

CCI [redacted]

[1] Doses in Part 2 may be adjusted based on preliminary analyses of exposure and response data from Part 1. As a result, the dosing instructions and the placebo match in Part 2 would then be aligned to the specific dose regimen that is chosen.

Table 5 VH4011499 study arms

Arm Title	VH4011499	VH4011499	Placebo for VH4011499	VH4011499	Placebo for VH4011499
Part	Part 1b	Part 1b	Part 1b	Part 2b	Part 2b
Arm Type	Experimental	Experimental	Placebo	Experimental	Placebo
Regimen	6	7	8	9	10

CCI [redacted]

[1] Doses in Part 2 may be adjusted based on preliminary analyses of exposure and response data from Part 1. As a result, the dosing instructions and the placebo match in Part 2 would then be aligned to the specific dose regimen 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 or authorized site staff are 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 VH/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. CCI [redacted]. Unused study intervention tablets in opened bottles may not be offered to the study participant beyond the expected dosing schedule as outlined in the SoA (Section 1.3) and may not be offered to any other person.

6.4. Blinding

This is a double-blind (sponsor unblinded) placebo-controlled study in which participants/investigators will not be unblinded to treatment (active capsid inhibitor drug or placebo) at the participant level. CCI [redacted]

CCI [redacted]

There is a theoretical concern that investigators may deduce treatment assignment during the monotherapy period since they will have access to HIV-1 RNA results from the monotherapy period. However, since this study is a proof-of-concept clinical trial rather than a confirmatory trial, insufficient anti-viral effect over the monotherapy period cannot reliably predict placebo assignment. The monotherapy period is short which minimizes the likelihood of bias on subsequent endpoints during the monotherapy period. Knowledge of the treatment received during the monotherapy period is of little consequence within the SOC period and has no impact on the future conduct of the trial or assessment of study endpoints.

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.

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 9.5 for more details about preservation of the blind during the conduct of the informal planned interim analyses. VH/GSK global safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or VH/GSK policy. A participant may continue in the study if that participant's intervention assignment is unblinded.

6.5. Study intervention compliance

Participants will receive study intervention directly from qualified site staff and CCI [redacted] The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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 the investigational CAI (VH4004280 or VH4011499) after the end of the study is not permitted since therapeutic benefit has not yet been established.

The investigator is responsible for ensuring consideration has been given to the poststudy care and treatment of the participant's medical condition. The Sponsor recognizes some HIV-1 infected adults may encounter barriers to timely access to cART. Where it has been determined by the investigator to be an acceptable option, participants who have completed the study (i.e., Day 39 EOS which includes 10 days of double-blind monotherapy and 4 weeks of investigator chosen SOC) and are exercising reimbursement assistance from the Sponsor for their SOC, will have the option (but are not required) to receive up to an additional 3 months of reimbursement assistance post study. The investigator will choose the standard of care cART according to local treatment guidelines, accessibility and locally run genotypic/phenotypic results (if available).

6.8. Treatment of overdose

For this study, any dose of the CAI study intervention that exceeds the specified dose for that treatment group will be considered an overdose. In the event of an overdose, the investigator should:

- Contact the VH medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically, as medically appropriate.
- If requested by the VH medical monitor, obtain a plasma sample for PK analysis as soon as possible after the overdose. Intensive and single PK sampling is pre-specified as per the SoA (Section 1.3) such that an additional PK sample in the event of overdose may not be needed.
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding investigations and management will be made by the investigator in consultation with the VH medical monitor based on the clinical evaluation of the participant, although VH/GSK does not recommend specific treatment for an overdose.

Refer to the approved product label for the cART standard of care for advice on overdose.

6.9. Prior and concomitant therapy

The VH medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with reason for use, dates of administration including start and end dates, and dosage information including dose and frequency.

- Acetaminophen/paracetamol at doses of ≤2 grams/day or nonsteroidal anti-inflammatory drugs (NSAIDs) are permitted for use any time during the study and their use documented in the CRF.

CCI [redacted]

- No clinically significant interactions are expected following the start of any anticipated cART standard of care regimen on Day 11.

CCI [redacted]

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 CCI [redacted]

Despite the study intervention being 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 cART standard of care on Day 11) and be followed according to the SoA (Section 1.3) to the EOS as defined in the protocol. CCI [redacted]

If participants prematurely discontinue study treatment prior to Day 11 (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 7.1.1 (Liver chemistry stopping criteria), Section 7.1.2 (QTc stopping criteria) and Section 7.2.1 (SARS-CoV-2 management criteria).

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	
Death	
Participant Reached Protocol-Defined Stopping Criteria	Specify
Lack of efficacy	
Lost to follow-up	
Physician Decision	Specify
Protocol Deviation	Specify
Withdrawal by Participant	Specify
Other	Specify

7.1.1. Liver chemistry stopping criteria

Liver stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology, in alignment with the FDA premarketing clinical liver safety guidance:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

If a participant meets the liver chemistry stopping criteria (i.e., ALT≥3xULN) further CAI dosing should be discontinued if applicable CCI [redacted] and the participant will be monitored as detailed in Section 10.6.

CCI [redacted] In the presence of abnormal liver chemistries that do not meet the protocol-specified liver chemistry stopping rule, the investigator may choose to discontinue further study treatment 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.

7.1.2. QTc stopping criteria

A participant that meets any of the bulleted criterion based on the average of triplicate ECG readings will have met a QTc stopping criterion.

- QTcF >500 msec,
- Change from baseline: QTcF >60 msec

If a QTc stopping criteria is met or another clinically significant finding is identified, then the investigator in consultation with the VH medical monitor will determine if any change in participant management is needed and if the participant can continue the study intervention. Any new clinically relevant finding should be reported as an AE.

Refer to Section 8.3.7 for information about study pausing criteria.

7.1.3. Pregnancy

Participants who become pregnant during the study should discontinue. Refer to Section 8.4.5 for further details.

7.1.4. Temporary discontinuation

Temporary discontinuation of either VH4004280/placebo or VH4011499/placebo is not allowed in this study.

7.1.5. Rechallenge

Rechallenge with either VH4004280/placebo or VH4011499/placebo is not allowed in this study.

7.2. Participant discontinuation/withdrawal from the study

- A participant may withdraw from the study at any time at their own request for any reason (or without providing any reason) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance 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 cART standard of care on Day 11) 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, with the exception of SARS-CoV-2 scenarios as described in Section 7.2.1. If participants prematurely discontinue the study for non-safety reasons prior to Day 11 (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 contact participants who do not return for scheduled visits or follow-up and encourage protocol compliance.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). The SoA lists the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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. 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 (refer to Section 10.3.6).

7.2.1. SARS-COV-2 Management Criteria

A participant who is found to have SARS-CoV-2 infection during the study may proceed in the study at the discretion of the investigator and sponsor assuming the participant isolates according to current Centers for Disease Control and Prevention guidance and then has a repeat SARS-CoV-2 test that is negative. Otherwise, participants who are withdrawn from the study due to SARS-CoV-2 infection (including exposure to SARS-CoV-2) may be replaced based upon the discretion of the sponsor and investigator.

Refer to Section 10.9 for further details regarding the conduct of the study when impacted by SARS-CoV-2 infections and/or exposures.

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:

1. 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.
2. 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.
3. Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
4. 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

5. Study procedures and their timing are summarized in the Schedule of activities (SoA) (Section 1.3). Protocol waivers or exemptions are not allowed.
6. Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
7. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
8. 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 (Section 1.3).

9. 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. Refer to Section 10.10 for more information.
10. The maximum amount of blood collected from each participant over the duration of any 56-day period will not exceed 500 mL.
11. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
12. Pharmacokinetic results that could unblind the study will not be reported to investigative sites or other blinded personnel.

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 intended 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. Also obtain the participant's SARS-CoV-2 vaccination history. 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 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 (Section 1.3).

8.3.1. 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 is symptom driven (with the exception of an expected respiratory system assessment at select visits) and may be targeted to include select system/organ assessments. 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 body mass index (BMI).

8.3.2. Vital signs

- Vital signs (to be taken before blood collection for laboratory tests) will consist of body temperature, single pulse rate, respiratory rate and blood pressure measurement.
- 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 (e.g., television, cell phones). 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

Single 12-lead ECG tracings will be obtained as outlined in the SoA (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.

Under certain circumstances 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 7.1.2 for QTc stopping criteria for further details.

8.3.4. Clinical safety laboratory tests

- Refer to Section 10.2 for the list of clinical safety laboratory tests to be performed by the central laboratory in accordance with the Lab Manual and the SoA (Section 1.3). 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 point of care SARS-CoV-2 validated test will be run locally to determine eligibility on Day 1. Sites should adhere to the manufacturers guidance for which samples are allowed (e.g., nasopharyngeal, oropharyngeal).
- 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.
- All laboratory tests with values considered clinically significantly abnormal from dosing of the study intervention until the EoS visit (i.e., Day 39) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or VH 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

- Participants of childbearing potential (POCBP) must perform a pregnancy test before the administration of any dose of study intervention. 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.
- Serum samples will be sent for pregnancy testing for the Screening Visit and all other timepoints. 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.

Additionally at the Day 1 Visit, a serum sample will be sent for pregnancy testing at the same time.

- Refer to Section 8.4.5 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Suicidal ideation and behavior risk monitoring

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

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicidality Severity Rating Scale (C-SSRS). The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months); all subsequent questioning is in relation to the last assessment. The eC-SSRS questionnaire is to be administered by a clinician at the timepoints in the SoA (Section 1.3). The eC-SSRS will be conducted electronically by computer.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal 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 VH medical monitor and the GSK safety lead. 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, the ViiV Safety and Labelling Committee (VSLC) 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 following study pausing criteria would be applied per compound:

- Any SAE, regardless of its severity, that is considered to be clinically significant and reasonably attributable to dosing with VH4004280 or VH4011499, in the opinion of the investigator or the Sponsor.
- Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement that the investigator considers reasonably attributable to VH4004280 or VH4011499.
- Any Grade 4 AE or laboratory abnormalities (with the exception of an asymptomatic Grade 4 lipid abnormalities or CPK increase) that the investigator considers reasonably attributable to VH4004280 or VH4011499.
- Any participant meeting liver stopping criteria that the investigator considers reasonably attributable to VH4004280 or VH4011499.
- Any participant meeting QTc stopping criteria that the investigator considers reasonably attributable to VH4004280 or VH4011499.

8.4. Adverse Events (AEs) and serious adverse events (SAEs)

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 (Section 6.9). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

8.4.1. Time period and frequency for collecting AEs and SAEs

All SAEs will be collected from the signing of the ICF until the final follow up visit. All AEs will be collected from the start of study intervention 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/pregnancies 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. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available

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

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

Contacts for SAE reporting can be found in Section 8.4.8.

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 Section 10.3.6.6.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the CIBs 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

To be eligible to participate in the study, participants who were female at birth must not be pregnant (i.e., must have a negative pregnancy test) nor breastfeeding. In addition,

POCBP must be using acceptable forms of birth control from Screening through to Day 39. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a POCBP with an early undetected pregnancy. Study intervention may only be administered if the screening pregnancy test (blood) and an additional pregnancy test on Day 1 (urine) are negative. Pregnancy testing for POCBP must be performed post baseline as per the SoA (Section 1.3).

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until Day 39.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor. See Section 8.4.1 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/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- 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.

8.4.6. CV and death events

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

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

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

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

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.8) 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 Disease Related Event on the SAE page rather than the HIV Associated Conditions eCRF.

8.4.8. Contact information for reporting SAEs, pregnancies and study stopping criteria

As per Section 10.3.6.7, 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 to report the event within 24 hours. Refer to Table 6 if you have questions.

Table 6 Contact information for safety events questions and/or reporting

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

8.5. Pharmacokinetics

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

CCI [redacted]

- Otherwise on single PK draw days 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 for CCI, dosing and PK draws for intensive PK days.

Table 7 Intensive Pharmacokinetic Sampling Schedule on Day of Dosing

	Time of Event	Window	Time Relative to Dosing Hour:Minute
	CCI [redacted]		
Dosing Day	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.

  - 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 VH4004280 or VH4011499 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 of the Participant

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

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

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Laboratory Manual.

8.8. Biomarkers - Viral Genotyping and Phenotyping

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 11 will be batch tested for viral genotypic and phenotypic on treatment changes and/or resistance to the CAIs 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 cART. 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 assessments are not evaluated in this study.

8.10. Health economics

Health economic parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to DBL 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 secondary endpoints. If methods in the SAP differ from the methods described in the protocol, the SAP prevails.

9.1. Statistical hypotheses

The primary objective, as outlined in Section 3, 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 for each dose for both VH4004280 and VH4011499 CAIs.

9.2. Statistical hypotheses

The primary objective, as outlined in Section 3, 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 for each dose for both VH4004280 and VH4011499 CAIs.

9.3. Analysis sets

Analysis Set	Definition
Screened	• All participants who are screened for eligibility
Randomized	• All participants who are randomly assigned to study treatment (i.e., VH4004280, VH4011499 or placebo) in the study
Safety	• All randomized participants who take at least 1 partial or full dose of study treatment • Participants will be analyzed according to the treatment they actually received
Full Analysis Set (FAS)	• All randomized participants who received at least one full dose of study treatment • Data will be reported according to the randomized study intervention
Per-Protocol (PP)	• All participants in the full analysis set for whom there were no major protocol deviations that impact the primary analyses • Data will be reported according to the treatment actually received • Specific details of major protocol deviations that would exclude participants from the PP analysis set will be provided in the SAP
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 treatment

Further analysis sets may be defined in the SAP, as needed.

9.4. Statistical analyses

9.4.1. General considerations/definitions

Data will be summarized by treatment (i.e., VH4004280, VH4011499, placebo matching VH4004280 and placebo matching VH4011499) 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, standard deviation (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

9.4.1.1. Protocol Deviations leading to exclusion from PP analysis set

The SAP will describe the major protocol deviations that would exclude a participant from the Per Protocol analysis set.

9.4.2. Primary endpoint/estimand analysis

See Section 3 for definition of primary endpoint and estimand.

9.4.2.1. Definition of endpoint/estimand

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 log10 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 log10 scales. The log10 transformation is used to allow for direct comparisons with data from other compounds publicly available in the same scale, and hence aid in interpretation.

9.4.2.2. 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 treatment (i.e., VH4004280, VH4011499, placebo matching VH4004280 and placebo matching VH4011499) and dose level, in original and log10 scales.

In addition, change from Baseline in plasma HIV-1 RNA at each assessment time point during monotherapy will be summarized by treatment and dose level, in original and log10 scales.

Descriptive statistics will be provided as described in Section 9.4.1.

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

Any missing HIV-1 RNA data (e.g., due to missed visits in the clinic, LFU or for any other reason) will not be imputed and will remain missing. Whatever HIV-1 RNA data are available for a participant during monotherapy and prior to starting SOC will be used to calculate maximum VLD.

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.

9.4.2.3. Supplementary/supportive analysis/analyses

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

9.4.3. Secondary endpoints/estimands analyses

See Section 3 for definition of secondary endpoints and estimands.

9.4.3.1. 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.

Analysis Method

The number and proportion of participants with AEs will be tabulated overall and by severity grade, by treatment and dose level. The number and proportion of participants with AEs leading to discontinuation of VH4011499 or placebo matching VH4011499 will also be tabulated by dose level of VH4011499 and placebo (matching VH4011499). 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 (e.g., mean, median, std etc.) of change from Baseline values by visit will be presented by treatment and dose level. Number and percentage of participants with maximum toxicity grade increase from Baseline for liver panel parameters will be presented by treatment and dose level; this will be done separately for the monotherapy period and overall (i.e., monotherapy period plus SOC).

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

All available safety data will be considered in summaries of AEs and liver panel laboratory parameters within the respective period (e.g., monotherapy or monotherapy plus SOC) CCI [redacted] or prohibited medication use has occurred.

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

9.4.3.2. Pharmacokinetic analyses

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

Analysis Method

Pharmacokinetic analysis will be the responsibility of the CPMS Department at GSK. Plasma VH4004280 and VH4011499 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 8.1 or higher, Phoenix (Pharsight Corporation) or comparable software to derive the PK parameters. This analysis will be based on actual sampling times recorded during the study. The various PK parameters will be inferred as data permits. Individual plasma PK parameters for each participant will be determined, including but not limited to Cmax and tmax.

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 treatment (i.e., VH4004280 and VH4011499) and dose level. PK parameters will be summarized descriptively by treatment (i.e., VH4004280 and VH4011499) and dose level. Descriptive summaries will be used as described in Section 9.4.1.

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.

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

CCI [redacted]

Additional estimands for PK analyses may be specified in the SAP.

CCI [redacted]

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

9.4.3.3. Pharmacokinetic-Pharmacodynamic analyses

Analysis Method

The relationship between selected PK parameters (e.g., concentrations on Day 11) 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. No imputation will be performed for missing data.

9.4.4. Exploratory endpoints/estimands analysis

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

9.5. Interim analyses

An informal planned interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1a have completed their Day 11 visit. A second informal planned interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1b have completed their Day 11 visit.

The planned interim analyses will evaluate the PK and pharmacodynamic (antiviral activity) of each respective capsid inhibitor and inform if a third pre-specified optional dosing arm for each capsid inhibitor will be evaluated in Part 2. Depending on the Part 1 results, a higher dose, lower dose, or a dose between the two doses evaluated in Part 1 will be evaluated in Part 2. It is also possible that Part 2 will not be conducted for one or both capsid inhibitors if the doses evaluated in Part 1 adequately describe the exposure-response of each capsid inhibitor. The interim results will also inform future clinical development of both compounds.

CCI [redacted]

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 39 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.

9.6. Sample size determination

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

9.6.1. Sample Size Considerations

Based on data from the top two doses of the short-term monotherapy study of CCI [redacted] we assumed the maximum viral load decline (VLD) from Baseline in log10 scale for individual participants follows a normal distribution.

Assuming normality, the sample size of N=6 participants per intervention cohort allows estimation of the mean maximum VLD in log10 scale with precision shown on Table 8. Table 8 shows the expected precision of the estimated mean maximum VLD in log10 scale measured by the 95% CI width for various observed data variability assumptions as reflected by the sample standard deviation (SD).

Table 8 CCI [redacted]

9.6.2. Sample Size Sensitivity

To evaluate study's sensitivity to sample size we calculated the expected precision of the estimated mean of maximum VLD in log10 scale for a treatment intervention for various sample sizes. Figure 2 shows the expected precision, measured by the 95% CI width, of the estimated mean maximum VLD in log10 scale for various sample sizes for a

treatment intervention and various assumptions on the observed data variability (reflected by the sample SD).

Figure 2

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.
- Any 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, 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.

If partners of male participants become pregnant during the study, consent will need to be obtained or notification given as per local regulation to the partner before collecting their PI (such as LMP and year of birth) or the PI of their baby (such as date of birth and sex) as part of safety follow-up.

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 VH/GSK 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. Committees structure

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

The SRT is in place for each VH product and is comprised 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 studies of both CAIs.

ViiV Healthcare's 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.

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 and/or PPD 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 protocol summaries prior to study start and target results summaries submission within 12 months after the study end in all countries in the study.
- 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 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. 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.

Local safety laboratory results are only required if the investigator anticipates that the central laboratory results will not be available in time to support the administration of study intervention and/or to properly evaluate the participant.

If a local safety sample is required, it is important that the sample for central analysis is obtained at the same time. If the central laboratory results significantly differ from the local results, then the local results will be transcribed into the eCRF (units, normal range and certification will need to be reported). If the central results corroborate the local results, then the local results will be retained in the source documents and not transcribed into the eCRF. Local genotypic/phenotypic nor HIV-1 RNA results should be entered into the eCRF.

Table 9 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Coagulation	Prothrombin time (PT) Partial thromboplastin time (PTT) International normalized ratio (INR)	
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell (RBC) count	
	RBC indices	Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Percent reticulocytes
	White blood cell (WBC) count with differential	Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Amylase Lipase Creatine phosphokinase (CPK)[2] Glucose Calcium Sodium Potassium Blood urea nitrogen (BUN) Creatinine[3]	

Laboratory Assessments	Parameters
	Total protein Total and direct bilirubin Alkaline phosphatase[4] Aspartate aminotransferase (AST or SGOT) Alanine aminotransferase (ALT or SGPT) Total Bile Acid (TBA)
Lipid Panel (fasting)	Triglycerides Total cholesterol Low-density lipoprotein (LDL) cholesterol High-density lipoprotein (HDL) cholesterol
Routine Urinalysis	Specific gravity Dipstick (pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase) Microscopic examination (if blood or protein is abnormal) to include epithelial cells, RBCs, WBCs, casts, crystals and a culture (if positive, specify pathogen).
Other Tests	• Highly sensitive (serum or urine) human chorionic gonadotropin (hCG) pregnancy test participants female at birth • Follicle-stimulating hormone, if needed to demonstrate that a female is of nonchildbearing potential (See Section 10.4) • 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, hepatitis B surface antigen [HBsAg], Hepatitis B Core antibody (anti-HBc), 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)

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.6. 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 an expedited manner (excluding studies of hepatic impairment or cirrhosis). Laboratory analytes to be tested will include the routine liver panel and additional analytes [such as lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin].
2. 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.
3. Estimated serum creatinine clearance (using the Chronic Kidney Disease Epidemiology Collaboration CKD-EPI method [Delgado, 2021].
4. at screening for eligibility determination ([creatinine clearance (eGFR) of < 50 mL/min/1.73 m^2].
5. If alkaline phosphatase is elevated, consider fractionating.

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 <u>NOT</u> 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 8.4.9):
  - 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.
- As AEs will not be solicited in this study, no list of solicited events is specified in this protocol.

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 one of the following categories according to the DAIDS toxicity scales (refer to Section 10.7).

Where a DAIDS toxicity scale is not available for a particular event or parameter, then the investigator will instead make an assessment of intensity using one of the severity categories described in the functional DAIDS table shown in Section 10.7.

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

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

10.3.6.3. 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 CIBs 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.
- 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 8.4.3).

10.3.6.7. Reporting of SAE 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 VH/GSK non-IMP they will

report these events to VH/GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

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

SAE Reporting to VH/GSK via Paper Data Collection Tool

- Email 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 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.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Participant of childbearing potential

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. Participants of nonchildbearing potential

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.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L is required.

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

10.4.2. Contraception guidance

10.4.2.1. Participants of childbearing potential

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

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.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
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 c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. 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)

10.4.2.2. Participants assigned as male at birth

Male participants must agree to use contraception/barrier as detailed below:

- **Agree to use a male condom** and should also be advised that a female partner (if of child-bearing potential) to use a highly effective method of contraception with a failure rate of <1%.

AND

- **Partner of child-bearing potential to use an additional highly effective contraceptive method** (with a failure rate of <1%) that has a low user dependency or that is user dependent.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY FOR PARTNERS OF CHILD-BEARING POTENTIAL INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
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 c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Genetics

The potential use and analysis of DNA samples is explained as follows:

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to the CAI study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a [blood/saliva] sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to VH4004280, VH4011499 or HIV and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to VH4004280, VH4011499, interventions of this drug class and/or HIV disease. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to VH4004280, VH4011499 or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on VH4004280, VH4011499 or other CAIs of HIV-1 continues but no longer than 15 years or other period as per local requirements.

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

Phase 2a liver chemistry monitoring criteria have been designed to assure participant safety and to evaluate liver event etiology. In addition, see Section 8.3.7 (Clinical criteria for pausing and/or stopping the study).

Phase 2a Liver Chemistry Monitoring/Stopping Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Monitoring/Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN

Report the following as an SAE[1,2]:

• ALT≥3xULN AND total bilirubin≥2xULN (>35% direct bilirubin) or

• ALT≥3xULN AND international normalized ratio (INR) >1.5</td></tr>
<tr><th colspan="3">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue CAI study intervention, if applicable, and do not restart.

• Report the event to VH medical monitor within 24 hours. Follow SAE reporting requirements if applicable.

• Complete the liver event eCRF 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.

• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING).

MONITORING:

If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5</td><td colspan="2">Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below:

• Viral hepatitis serology[3]

• Syphilis screening

• Drugs of abuse screen, including alcohol

• Obtain international normalized ratio (INR)[2] and recheck with each liver chemistry assessment until the aminotransferases values show downward trend

• Obtain blood sample for pharmacokinetic (PK) analysis within 60 hours of last dose or as soon as possible in relation to the most recent dose. Additional samples can be obtained as needed as dependent on the medical guidance[4]

• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH),</td></tr>
</table>

Liver Chemistry Monitoring/Stopping Criteria	
• Repeat liver chemistries (include ALT, aspartate transaminase [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, stabilise or return to within baseline. • A specialist or hepatology consultation is recommended. **If ALT≥3xULN AND total bilirubin < 2xULN 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.	gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin. • Fractionate bilirubin[1] 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 eCRF form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications • Record alcohol use on the liver event alcohol intake eCRF 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 Chemistry Monitoring/Stopping Criteria	
	• Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy[5] to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

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 ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; hepatitis E IgM antibody; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and.
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of CAI 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 laboratory manual.
5. Liver biopsy may be considered and discussed with local specialists if available, for instance:
    - In participants when serology raises the possibility of autoimmune hepatitis (AIH).
    - In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention.
    - In participants with acute or chronic atypical presentation.

10.7. Appendix 7: Division of AIDS table for grading the severity of adult and pediatric adverse events

CORRECTED VERSION 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("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.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

Table 10 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.

Table 10 DAIDS grading for an AE that is not specifically identified in the grading table

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

For more information, please refer to the DAIDS grading table corrected version 2.1, July 2017 [DAIDS, 2017].

10.8. Appendix 8: 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 oesophagus

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

Source: [CDC, 2014]

10.9. Appendix 9: Permissible Procedures During COVID-19 Pandemic

Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the study intervention or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the study intervention or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until the site is able to resume normal working activities and may be re-instated as warranted.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, the investigator should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

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

- Investigators should document in site files how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.
- Participants previously deemed eligible during the screening period unable to attend within the allowable screening window due to COVID-19 may be rescreened.
- A participant who is found to have SARS-CoV-2 infection during the study may proceed in the study at the discretion of the investigator and sponsor assuming the participant isolates according to current Centers for Disease Control and Prevention guidance and then has a repeat SARS-CoV-2 test that is negative.

- Participants who are withdrawn from the study due to COVID-19 infection (including exposure to COVID-19) may be replaced based upon the discretion of the sponsor and investigator.

Vaccination for SARS-CoV-2

Vaccination with an approved vaccine for SARS-CoV-2 is not permitted during the study but may occur at least 14 days prior to dosing on Day 1 or after Day 39/Early Discontinuation Visit.

Data Management/Monitoring:

- If on-site monitoring is no longer permitted, VH/GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, VH/GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The investigator is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The investigator may sign/re-sign the eCRF from any computer/location by accessing the eCRF using his/her unique eCRF log-in credentials. The investigator may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by VH/GSK.

10.10. Appendix 10: Country-specific requirements

10.10.1. Specific requirements for France

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the «SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

The following vulnerable subject populations will be excluded of compensation for the inconvenience of participating in the study: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1).

It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject is affiliated to or beneficiary of a social security category.

Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the Informed Consent Form. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.

According to French Public Health Code (L.1121-16 and R.1121-16), the following people must be registered in National File ("Fichier National"):

- Healthy volunteer;
- Subjects if the aim of the study is not linked to their disease;
- Subjects on request of the Ethics Committee regarding study risks and constraints.

The following details will be described:

- Reference of the study
- Surname and first name
- Date and place of birth
- Gender
- Dates of beginning and termination of the study
- Exclusion period during which the subject cannot participate to another study (French Public Health Code L.1121-12)

- The total amount of compensation, if any.

The subjects' registration in National File ("Fichier National") should be documented in the source document - subject notes and monitored by the CRA.

2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

⇒ Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the single scientific and ethical regulatory authorization.

⇒ **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **Notification to the hospital director**

In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **Information to the hospital pharmacist**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

3. Concerning the "DATA MANAGEMENT" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in VH/GSK data bases by VH/GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through VH/GSK (Clinical Operations Department).

- **Ethnic Origin**

  In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **Testing of Biological Samples**

  In accordance with the French Public Health Code – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with VH/GSK in accordance with the legal provisions.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 08-May-2023 14:59:42 GMT+0000

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