Protocol Amendment 1

Study ID: 218490

Official Title of the Study: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Orally Administered VH4011499 in Healthy Participants.

NCT Number: NCT05393271

Date of Document: 14 November 2022

TITLE PAGE

Protocol Title: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Orally Administered VH4011499 in Healthy Participants.
Protocol Number: 218490 / Amendment 01
Compound Number or Name: GSK4011499 (also known as VH4011499)
Brief Title: VH4011499 First-Time-in-Human-Study
Study Phase: Phase 1
Sponsor Name and Legal Registered Address:

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This study is sponsored by ViiV Healthcare. GSK is supporting ViiV Healthcare in the conduct of this study.

Regulatory Agency Identifying Number(s): Regulatory Agency identifying number(s) as appropriate

Registry: IND ID: 159876

Sponsor Signatory

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Approval Date: 14 Nov 2022
Medical Monitor Name and Contact Information can be found in the Study Reference Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	14 Nov 2022
Original Protocol	13 April 2022

Amendment 01 14 Nov 2022

Overall Rationale for the Amendment: This amendment results from the FDA "Study May Proceed" letter for IND Opening (Number 159876, Reference ID 4981945) dated 13-MAY-2022, wherein the FDA recommended that the inclusion of women of childbearing potential be considered but require the use of highly effective forms of contraception, excluding modalities that may have potential DDIs. Additionally, this amendment results from Sponsor decisions to include an evaluation of the VH4011499 tablet formulation for comparison with the existing VH4011499 PiB data and any potential perpetrator risks of DDIs associated with CYP3A4 inhibition and induction and OATP1B1/1B3 inhibition. An additional optional MAD dosing group (Optional MAD Dosing Group 4) is being added and MAD Dosing Group 3 is being required by the Sponsor in response to the inclusion of DDI evaluations. Part 3 of the study was included to evaluate the safety, tolerability and pharmacokinetics of the VH4011499 tablet formulation. Lastly, points of clarification have been incorporated throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 (Synopsis)	Updates supporting the addition of midazolam intervention as a sensitive CYP3A4 probe substrate and the evaluation of an endogenous biomarker (coproporphyrin I) as a OATP1B1/1B3 probe substrate in Part 2. Updates supporting the addition of a dosing group (Part 3) to evaluate a VH4011499 tablet formulation in comparison with existing data from VH4011499 PiB. Updates supporting the requirement of MAD Dosing Group 3 and the addition of an optional MAD Dosing Group (Optional MAD Dosing Group 4). Updated primary endpoint to define the "liver panel". Liver panel includes total bilirubin, direct bilirubin, alkaline phosphatase, AST, and ALT.	Revision to evaluate the potential perpetrator risks of VH4011499 associated with CYP3A4 inhibition and induction and OATP1B1/1B3 inhibition. Revision to evaluate the safety, tolerability and PK properties of VH4011499 tablets compared to existing data from PiB. Sponsor decision to evaluate VH4011499 in three MAD dosing groups and to potentially evaluate VH4011499 in an additional MAD dosing group based on observed PK and safety data. Clarification for statistical analyses.
Section 1.1 (Synopsis); Section 4.1.3 (Part 3 (Tablet PK)); 7.4.2 (Clinical Criteria for Pausing and/or Stopping the Study); 10.1.5 (Committees Structure (Safety and Dose Escalation Committee))	Clarifications and updates regarding the utilization of the SDEC to support the addition of a dosing group (Part 3) to evaluate a VH4011499 tablet formulation in comparison with existing data from VH4011499 PiB	Sponsor decision to utilize the SDEC to review data from Part 3.
Section 1.2 (Schema); Section 2.1 (Study Rationale); Section 4.1 (Overall Study Design); Section 4.2 (Scientific Rationale for Study Design); Section 4.3.7 (Tablet PK (Part 3) Dose Selection); Section 5.3 (Lifestyle Considerations)	Updates supporting the addition of midazolam intervention as a sensitive CYP3A4 probe substrate and the evaluation of an endogenous biomarker (coproporphyrin I) as a OATP1B1/1B3 probe substrate in Part 2. Updates supporting the addition of a dosing group (Part 3) to evaluate a VH4011499 tablet formulation in comparison with existing data from VH4011499 PiB. Updates supporting the requirement of MAD Dosing Group 3 and the addition of an optional MAD Dosing Group (Optional MAD Dosing Group 4).	Revision to evaluate the potential perpetrator risks of VH4011499 associated with CYP3A4 inhibition and induction and OATP1B1/1B3 inhibition. Revision to evaluate the safety, tolerability and PK properties of VH4011499 tablets compared to existing data from PiB. Sponsor decision evaluate VH4011499 in three MAD dosing groups and to potentially evaluate VH4011499 in an additional MAD dosing group based on observed PK and safety data.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of Activities (SOA))	Updates supporting the addition of midazolam intervention as a sensitive CYP3A4 probe substrate and the evaluation of an endogenous biomarker (coproporphyrin I) as a OATP1B1/1B3 probe substrate in Part 2. Updates supporting the addition of a dosing group (Part 3) to evaluate a VH4011499 tablet formulation in comparison with existing data from VH4011499 PiB. Updates supporting the requirement of MAD Dosing Group 3 and the addition of an optional MAD Dosing Group (Optional MAD Dosing Group 4). Inclusion of pregnancy testing throughout the study. Removal of a Plasma Sample (metabolism) assessment in Part 2 (all dosing groups) at specific timepoints.	Revision to evaluate the potential perpetrator risks of VH4011499 associated with CYP3A4 inhibition and induction and OATP1B1/1B3 inhibition. Revision to evaluate the safety, tolerability and PK properties of VH4011499 tablets compared to existing data from PiB. Sponsor decision to evaluate VH4011499 in three MAD dosing groups and to potentially evaluate VH4011499 in an additional MAD dosing group based on observed PK and safety data. FDA Recommended Change, Clinical item #1. Sponsor driven clarification as this sample collection was not needed at all previously marked timepoints.
Section 2.3 (Benefit/Risk Assessment)	Updates to risk assessment summarizing new potential drug-drug interaction risks with VH4011499 and midazolam introduced with the new study design.	To align with conduct of the updated study design.
Section 3 (Objectives and Endpoints)	Updates to objectives and endpoints in alignment with conduct of the updated study design. Updated primary endpoint to define the “liver panel”. Liver panel includes total bilirubin, direct bilirubin, alkaline phosphatase, AST, and ALT.	Revision to evaluate the potential perpetrator risks of VH4011499 associated with CYP3A4 inhibition and induction and OATP1B1/1B3 inhibition. Revision to evaluate the safety, tolerability and PK properties of VH4011499 tablets compared to existing data from PiB. Clarification for statistical analyses.
Section 4.1.2 (Part 2 (MAD)); Section 4.3.3 (Top Dose Rationale); Section 4.3.6 (Repeat Dosing Plan (Part 2))	Updates to reflect decision to include NOAEL as an additional, independent criterion for top dose determination in MAD (Part 2) dose escalations	Sponsor driven decision to amend dose escalation criteria.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 (Inclusion Criteria); Section 8.2.5 (Pregnancy Testing); Section 8.3.5 (Pregnancy); Section 10.4 (Appendix 4: Contraceptive and Barrier Guidance)	Updated to support the inclusion of WOCBP with the requirement that they use low user-dependency, highly effective (<1% failure rate) methods of contraception (IUD/IUS) or have bilateral tubal occlusion).	FDA Recommended Change, Clinical item #1.
Section 5.1 (Inclusion Criteria)	Revised inclusion criterion #5 to remove the option for male participants to agree to use a male condom and should also be advised of the benefit for a female partner of child-bearing potential to use a highly effective method of contraception.	Sponsor decision to take a more conservative approach and require highly effective contraception use in female partners of child-bearing potential of male participants and to rectify a discrepancy between inclusion criteria #5 and Appendix 4.
Section 5.2 (Exclusion Criteria)	Revised exclusion criterion #7 to highlight examples of medications that are Cytochrome P450 enzyme inducers or inhibitors. Revised exclusion criterion #23 to include any sensitivities to the additional study intervention, midazolam.	To support the updated study design.
Section 6 (Study Drug(s) and Concomitant Therapy)	Updated to include details of midazolam for Part 2 (MAD) and VH4011499 tablets for Part 3 (Tablet PK).	To support the updated study design.
Section 7.4.1 (PK Stopping Criteria for SAD and MAD)	Updates to reflect decision to include NOAEL as an additional, independent criterion for top dose determination in MAD (Part 2) dose escalations Updates to use the most current NOAEL parameters for VH4011499 ((which are based on emerging non-clinical GLP toxicity data and defined in the SDEC charter) at the time of any dose escalation decision.	Sponsor driven decision to amend dose escalation criteria. Sponsor driven decision to include protocol flexibility to adopt the most current NOAEL parameters at the time of any dose escalation decision.
Section 8.2.2 (Vital Signs)	Details of pulse oximetry included as part of risk mitigation strategy of midazolam dosing. Revised to qualify that temperature measurement should be according to site standard.	Continuous pulse oximetry (15 minutes prior to midazolam dosing through 6 hours post midazolam dosing) included to monitor for the respiratory effects of midazolam, on probe substrate drug dosing days. To permit flexibility observed at study site.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.3.1 (12-Lead Safety ECGs)	Revision to require repeat ECGs in triplicate in the case that the Investigator determines an ECG abnormality as clinically significant or is unable to determine the significance of abnormalities.	Sponsor driven revision to allow more flexibility in study conduct and not require repeat ECGs in triplicate for abnormal readings that are determined as not clinically significant.
Section 8.4 (Pharmacokinetics); Section 8.6 (Biomarkers)	New information added regarding midazolam and coproporphyrin I sampling.	To support the updated study design.
Section 9 (Statistical Considerations)	Updated to include description of statistical analyses on new endpoints. A section on Bayesian simulation for dose escalation in MAD has been added. Sample Size Determination section has been updated to provide expected precision of estimates for DDI evaluations and Part 3 for the chosen sample sizes.	To support the updated study design.
Section 10.1.3 (Informed Consent Process)	Inclusion of text to further clarify that in the case of an unexpected pregnancy in female participants, participants will be informed that personal information of the baby will be collected as part of safety follow-up. Inclusion of text to further clarify that informed consent must be obtained from female partners of male participants if female partners become pregnant during the study and partners will be informed that personal information of the baby will be collected as part of safety follow-up.	To provide further clarification of the informed consent process and data collection in the case of unexpected pregnancy in female participants or female partners of male participants.
Not applicable	Other minor revisions that provide clarification.	To provide further clarification in study conduct.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Orally Administered VH4011499 in Healthy Participants.

Brief Title:

VH4011499 First-Time-in-Human-Study.

Rationale:

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. The current paradigm in the treatment of HIV-1 involves life-long therapy with multiple ARVs. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all ARV classes. Long- acting injectable versions of drugs are being developed to improve convenience by extending the dosing interval from every day to every month or longer. These therapeutic options hold great promise for future treatment and represent an emerging paradigm for the treatment and prevention of HIV-1 infection. An all long-acting ARV regimen that is dosed every month or longer offers many potential advantages over daily dosed regimens, including: improved ARV adherence, improved treatment satisfaction, and minimizing the patient's daily reminder of their HIV status.

The overall objective of the ViiV CAI clinical development program is to develop investigational VH4011499 (also known as GSK4011499) as a long-acting novel medicine that can be administered via injection every month or longer CCI [redacted] Either long-acting VH4011499-containing regimen would offer efficacy and safety comparable to currently available daily dosed ARV regimens yet improve both treatment adherence and quality of life through its less frequent dosing schedule. Of note, VH4011499 is ViiV's second capsid inhibitor in clinical development and is preceded by VH4004280 which is currently in Phase 1.

VH4011499 belongs to a novel class of ARV agents targeting a highly conserved region of the HIV-1 capsid protein. In-vitro experiments suggest its primary antiviral mechanism of action is derived from inhibition of a replication step early in the viral replication cycle prior to integration of the HIV-1 provirus into the host cell chromatin. VH4011499 also possesses a less potent late antiviral activity, reducing production of infectious virions from virus-producing cells.

There are currently no capsid inhibitors approved for the treatment of HIV infection, although clinical efficacy and a generally favorable safety profile has been demonstrated in an investigational capsid inhibitor currently in development. In cell culture, VH4011499 exhibited potent antiviral activity against a wide spectrum of HIV-1 isolates and subtypes and also demonstrated no cross-resistance with currently approved ARV classes. The potential to develop VH4011499 as a long-acting medicine is further supported by nonclinical studies (including rat and dog studies up to 28 days) that show a favorable toxicity, safety and PK profile for VH4011499.

This FTIH study is designed to gain information on the safety, tolerability and PK properties of oral VH4011499 when administered as PiB. This study will also evaluate the safety, tolerability and PK properties of VH4011499 when administered as an oral tablet. The potential in-vitro based perpetrator risks of DDIs associated with CYP3A4 inhibition and induction will also be evaluated by assessing the effect of VH4011499 on midazolam, a sensitive CYP3A4 probe substrate. The potential DDI risks associated with OATP1B1/1B3 inhibition will also be evaluated by assessing the effect of VH4011499 on an endogenous biomarker as a probe (coproporphyrin I). This study will enable further clinical development of VH4011499, including a Phase 2a PoC study in HIV-infected participants and a Phase 1 study of the long-acting injectable formulation of VH4011499.

Objectives and Endpoints and Estimands:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single (Parts 1 and 3) and multiple (Part 2) doses of VH4011499 in healthy participants.	• Incidence of adverse events (AEs), severity of AEs and proportion of participants who discontinue treatment due to AEs • Absolute values, change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters [consisting of total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)]
To describe the plasma PK characteristics of VH4011499 in healthy participants following single (Part 1) and multiple (Part 2) doses.	• Area under the plasma-concentration time curve (AUC): AUC(0-inf) for single dose and AUC(0-t) for repeat dose. • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life (t1/2) will be calculated for each part (Part 1 SAD and Part 2 MAD) as data in each part permits.

Overall Design:

Brief Summary:

This is a double-blind (sponsor unblinded), randomized, placebo-controlled, single and multiple-ascending-dose Phase 1 study to evaluate the safety, tolerability and pharmacokinetics of VH4011499, when administered as a PiB formulation, in healthy adult participants. This study will also evaluate the DDI potential of VH4011499 for inhibition of OATP1B1/1B3 and changes in CYP3A activity, and evaluate the safety, tolerability and PK of a VH4011499 tablet formulation in comparison with existing data from VH4011499 PiB. All doses will be administered orally. This study will be executed in 3 parts.

In Part 1, the proposed dosing schedule is designed to investigate SAD of VH4011499 in up to 6 dosing groups. In Part 2, the proposed dosing schedule is designed to investigate MAD of VH4011499 administered daily, for 14 days in up to 4 dosing groups. A midazolam probe will be administered with VH4011499 or placebo in up to two dosing groups in Part 2 (MAD/DDI dosing group(s)) to examine the potential of VH4011499 to inhibit or induce CYP3A activity. The MAD/DDI dosing group(s) will also include the collection of endogenous biomarker (coproporphyrin I) samples before and following repeat dose administration of VH4011499 or placebo to investigate the potential of VH4011499 to inhibit OATP1B1/1B3. Review of available data from previous SAD and emerging MAD dosing groups will determine if the DDI potential of VH4011499 will be evaluated in one or two MAD dosing groups.

Part 3 (Tablet PK) is an open-label, single-dose design to evaluate the safety, tolerability and PK properties of the tablet formulation of VH4011499, in comparison with existing data from VH4011499 PiB, in one dosing group.

A SDEC will govern dose escalation decisions, including the determination of subsequent doses, based on emerging safety and pharmacokinetic data. The SDEC will also govern the total duration of dosing and follow-up, which may be altered if actual PK parameters (such as half-life) differ significantly from predicted values.

Number of Participants:

A sufficient number of healthy adults will be screened to provide 8 participants for randomization (6:2 active: placebo) within each SAD dosing group. Within each MAD dosing group, up to 8 participants will be randomized (6:2 active: placebo). Within each MAD/DDI dosing group, up to 10 participants will be randomized (8:2 active: placebo). Overall, up to 48 participants (36 active:12 placebo) will be included in Part 1. and up to 36 participants (28 active:8 placebo) will be included in Part 2, in the case that two MAD/DDI dosing groups are needed. Up to 6 participants will be included in Part 3 (Tablet PK).

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the Sponsor. Assignment of replacement numbers will be detailed in the SRM.

Note: Enrolled means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process, passed screening and were randomized in the study. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Intervention Groups and Duration:

Study participants will have a screening visit within 30 days prior to the first dose of VH4011499 / PBO.

In Part 1 (SAD), participants will receive a single dose of VH4011499 or placebo (6:2) on Day 1. Sentinel dosing is included. Safety and PK assessments will be performed at timepoints specified in the SoA. Participants will remain in the clinic until completion of the Day 7 procedures and will return to the clinic on Days 14 and 21 for follow up procedures and a final follow up visit on Day 28.

In Part 2 (MAD) participants will receive doses of VH4011499 or PBO once daily for an anticipated 14-day period. Participants in non-DDI MAD dosing groups will receive daily doses of VH4011499 or PBO (6:2) on Day 1 through Day 14 and will remain in the clinic until completion of the Day 21 procedures and will return to the clinic on Days 28 and 35 for follow up procedures and a final follow up visit on Day 42. In MAD/DDI dosing group(s), participants will receive a single dose of midazolam on Days 1, 2, and 15, and daily doses of VH4011499 or PBO (8:2) on Day 2 through to Day 15. A single dose of midazolam will be co-administered with a dose of VH4011499 or PBO on Days 2 and 15. Participants will remain in the clinic until completion of the Day 22 procedures and will return to the clinic on Days 28 and 35 for follow up procedures and a final follow up visit on Day 42.

In Part 3 (Tablet PK), participants will receive a single dose of VH4011499 as a tablet formulation on Day 1. The dose of VH4011499 to be administered in Part 3 will be determined based on review of available data from previous dosing groups in Parts 1 (SAD) and 2 (MAD) and predicted clinical doses. Participants will remain in the clinic until completion of the Day 7 procedures and will return to the clinic on Days 14 and 21 for follow up procedures and a final follow up visit on Day 28.

If actual PK parameters differ significantly from predicted values (e.g., if half-life is significantly longer or shorter than the predicted), then the duration of in clinic stay, duration of post last dose follow-up, determination of subsequent doses, dosing frequency and total duration of dosing may be altered. The duration of post dose follow-up is not intended to exceed five half-lives.

Data Monitoring/ Other Committee: Yes

The study will utilize a SDEC which will include, at a minimum, the Sponsor medical monitor, clinical pharmacologist, and statistician to meet with the Investigator to make a dose escalation decision. Limited additional Sponsor representatives may be included

on the SDEC. The decision to proceed to the next dose level of VH4011499 in both Part 1 (SAD) and Part 2 (MAD) will be made by the SDEC as outlined in the SDEC Charter, based on safety, tolerability and PK data obtained from the prior dose level(s). The study will also utilize a SDEC for instream reviews of emerging safety, tolerability and PK data during Part 3

1.2. Schema

PART 1 6 VH4011499: 2 PBO	SAD Dosing Group 1 (n=8)	SAD Dosing Group 2 (n=8)	SAD Dosing Group 3 (n=8)	SAD Dosing Group 4 (n=8)	Optional SAD Dosing Group 5 (n=8)	Optional SAD Dosing Group 6 (n=8)
Single PiB Solution Dose	25 mg	To be confirmed from elapsed PK	To be confirmed from elapsed PK	To be confirmed from elapsed PK	As required	As required

PART 2	MAD Dosing Group 1 (n=8) (6 VH4011499: 2 PBO)	MAD Dosing Group 2* (n=8 or n=10) (6 or 8 VH4011499: 2 PBO)	MAD Dosing Group 3* (n=8 or n=10) (6 or 8 VH4011499: 2 PBO)	Optional MAD Dosing Group 4 (n=8) (6 VH4011499: 2 PBO)
Once daily (QD) PiB Solution Dose	• > anticipated therapeutic dose at steady state • < NOAEL	< NOAEL	< NOAEL	As required

*DDI evaluation in one or two dosing groups, requiring midazolam (MDZ) probe administration, will be determined by emerging data
For this dosing group(s):
• MDZ dosed on D1, VH4011499 dosed QD 14 days (D2-D15), MDZ + VH4011499 on D2 and D15
• 10 participants will be enrolled (8 VH4011499: 2 PBO)

PART 3 6 VH4011499	Tablet PK Dose Group 1 (n=6)	Note: Dose will be within the predicted range of doses to be evaluated in future studies.
Single Tablet Dose	Dose determined following review of available data from Part 1 and Part 2	

PBO = placebo

Note: Actual doses (following Dosing Group 1) and the timing of transition from Part 1 (SAD) to Part 2 (MAD) will be informed by the emerging PK and safety data from previous dosing groups. Part 3 (Tablet PK) will be informed by available PK and safety data from previous dosing groups and predicted clinical doses CCI [redacted].

1.3. Schedule of Activities (SoA)

i. The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. These changes, if applicable will be determined at the discretion of the SDEC, the details of which are provided in the SDEC charter.

ii. Any changes in the timing of planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

iii. The Competent Authority and IEC/IRB will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the Competent Authority and the IEC/IRB before implementation.

iv. For further detail on Assessments and Procedures see Section 8.

Table 1 SCREENING AND EARLY DISCONTINUTION ASSESSMENTS (PART 1, PART 2, and PART 3)

Procedure	**Screening** (up to 30 days prior to Day 1)	**Early Discontinuation from Study Visit**	***Notes***
Outpatient Visit	X	X	
Informed Consent	X		
Inclusion and Exclusion Criteria	X		Additional tests may be performed by the Investigator, as deemed necessary to determine eligibility (e.g. where safety or laboratory findings indicate). Tests will be conducted according to site specific standards.
Demography	X		
Medical History	X		
Full Physical Examination (Including Height and Weight at the screening visit)	X		Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).
Brief Physical Examination and Weight		X	
12-lead ECG	X	X	Single ECGs will be used to determine participant eligibility at Screening.
Vital signs	X	X	
Drug/alcohol/cotinine screen	X		
HIV, Hep B and Hep C Screen	X		
Clinical Laboratory assessments	X	X	See Appendix 2: Clinical Laboratory Tests for details. Total bile acids at Early Discontinuation Visit. Fasting lipid panel at screening and at Early Discontinuation Visit.
Pregnancy Test	X	X	Highly sensitive serum hCG pregnancy test.
Follicle-stimulating Hormone	X		As required in women to confirm postmenopausal status.
SAR-CoV-2 PCR test	X[1]		Two consecutive SARS-CoV-2 PCR negative results are required prior to dosing. The tests should be performed on different days with the first test performed between Day -7 and Day -1 and the second test performed pre-dose.
Plasma pharmacokinetic sample		X	Not required if no study drug administered.
Adverse Event Review	X	X	The collection of SAEs will be from the screening visit to the end of the study. The collection of non-serious AEs will be from the start of study intervention until the end of the study.
Concomitant Medication Review	X	X	

Table 2 Part 1 Single Ascending Dose (SAD) (All Dosing Groups) - Inpatient Days -1 to 7

Procedure	Day																		
	Day -1	Day 1												2	3	4	5	6	7
		Pre-dose	0 h	0.5h	1 h	1.5 h	2h	3 h	4h	6 h	8h	10h	12h	24h	48h	72h	96h	120h	144h
Admission to Unit	X[9]																		
Discharge from Unit																			X
Drug/alcohol/cotinine screen	X																		
Brief Physical Exam[1]	X													X					X
Vital signs[2]	X	X			X		X		X		X		X	X	X	X	X	X	X
12-lead ECG[3]	X	X[4]			X				X				X	X	X		X		X
Cardiodynamic Assessment[3]		X[5]		<==========>[5]															
Meals		X		See Section 5.3.1															
Clinical Laboratory Tests[6,7,8]	X													X	X	X	X	X	X
SARS-CoV-2 PCR Test[9]	X[9]	X[9]																	X
Pregnancy Test[10]		X																	X
Randomization		X																	
Drug administration[11]			X																
Plasma Sample (pharmacokinetics)[12]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Day																	
	Day -1	Day 1												2	3	4	5	6	7
		Pre-dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	48 h	72 h	96 h	120h	144h
Plasma Sample (metabolism)[12]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample (metabolism)[13]		X		<==========>															
Adverse Event Review	<==========>																		
Concomitant Medication Review	<==========>																		

1. Brief physical exams may be made full physical exams at the discretion of the investigator.
2. Day 1 measured pre-dose; only blood pressure and pulse rate are measured for all remaining Day 1 timepoints.
3. See Section 8.2.3 for details of 12-lead ECGs and Cardiodynamic Assessment.
4. At pre-dose a triplicate 12-lead ECG is required within 90 minutes of dosing.
5. Three pre-dose ECG extractions prior to dosing on Day 1. Post-dose ECG extraction will coincide with plasma PK sample schedule up to 24h post-dose.
6. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests.
7. Total Bile Acids (TBA) and Coagulation Panel required on Day -1, Day 2 and Day 7 only.
8. Lipid Panel required on Day -1 and Day 7 only.
9. Two consecutive SARS-CoV-2 PCR negative results are required prior to dosing. The tests should be performed on different days with the first test performed between Day - 7 and Day -1 and the second test performed pre-dose. Admission to unit may be done on Day -2 if necessary for SARS-CoV-2 PCR testing.
10. See Section 8.2.5. Serum or urine pregnancy testing to be performed within 24 hours of dosing on Day 1.
11. In Part 1, VH4011499 will be administered as a PiB.
12. PK blood samples drawn post-dose should be collected on an approximately 24-hour cycle (i.e., 24 hours post last dose, 48 hours post last dose, 72 hours post last dose, etc)
13. A urine sample will be collected pre-dose (40 mL) within 1 h prior to dosing and from time 0 up to 24 h post dosing. Details of urine collection and processing are detailed in the SRM.

Table 3 Part 1 SAD (All Dosing Groups) - Outpatient Visit Days 14, 21 and 28

Procedure	Day		
	14	21	28[8]
Visit Window	±1 day	±1 day	±1 day
Brief Physical Exam[1]	X	X	X
Vital signs[2]	X	X	X
12-lead ECG[3]	X	X	X
Clinical Laboratory Test[4,5]	X	X	X
Pregnancy Test[6]	X	X	X
Plasma sample (pharmacokinetics)[7]	X	X	X
Adverse Event Review	<==========		==========>
Concomitant Medication Review	<==========		==========>

1. See Section 8.2.1 for details of brief physical exam. Brief physical exams may be made full physical exams at the discretion of the investigator. Weight will be measured on Day 28.
2. See Section 8.2.2 for details of Vital Sign measurements.
3. See Section 8.2.3 for details of 12-lead ECGs.
4. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests.
5. Total Bile Acids, Coagulation Panel and Lipid Panel to be included in each weekly clinical laboratory test.
6. See Section 8.2.5. Serum or urine pregnancy testing to be performed.
7. See Section 8.4 for further details for plasma PK sample collection. One whole blood sample of sufficient volume will be processed to measure concentrations of VH4011499.
8. In the event terminal half-life is longer than predicted, PK and laboratory assessment will occur every 7 days until an estimated 5 half-lives have elapsed.

Table 4 Part 2 Multiple Ascending Dose (MAD) - Inpatient Days -1 to 21

Procedure	Day																					
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Admission to Unit	X[1]																					
Discharge from Unit																						X
Drug/alcohol/cotinine screen	X																					
SARS-CoV-2 PCR Test[1]	X[1]	X[1]						X							X							X
Brief Physical Exam[2]	X							X							X							X
Vital Signs	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X	X	X	X	X	X
12-lead ECG[4]	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X[5]	X			X		X	X
Cardiodynamic Assessment[4]		<===>[6]													<===>[6]							
Meals		*See Section* 5.3.1																				
Clinical Laboratory Test[7,8,9]	X		X			X		X				X			X							X
Pregnancy Test[10]		X																				
Randomization		X																				
Drug Administration[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Plasma Sample (Pharmacokinetics)[12]		X[13]	X[14]	X[14]	X[14]	X[14]	X[14]		X[14]		X[14]		X[14]	X[14]	X[13]	X	X	X	X	X	X	X
Plasma Sample (metabolism)[12]		X[13]	X[14]												X[13]	X						
Urine Sample (metabolism)[15]		<===>													<=====>							
Bile Sample (EnteroTracker)[16]														X								
Adverse Event Review	<==========>																					
Concomitant Medication Review	<==========>																					

1. Two consecutive SARS-CoV-2 PCR negative results are required prior to dosing. The tests should be performed on different days with the first test performed between Day -7 and Day -1 and the second test performed pre-dose. Admission to unit may be done on Day -2 if necessary for SARS-CoV-2 PCR testing.
2. See Section 8.2.1 for details of brief physical examination. Brief physical exams may be made full physical exams at the discretion of the investigator.
3. Pre-dose and 1h, 3h, 6h and 12h. All vitals should be measured pre-dose; only blood pressure and pulse rate are measured for all remaining daily timepoints.
4. See Section.8.2.3 for details of 12-lead ECGs and cardiodynamic assessment (Holter monitoring).
5. Pre-dose triplicate ECG is required on Day 1 within 90 minutes of dosing. Dose administration day ECGs will be collected at pre-dose and 3, 6, 9 and 12-hours post-dose.
6. Three pre-dose ECG extractions prior to dosing on Day 1. Post-dose ECG extraction will coincide with plasma PK sample schedule up to 24h post-dose. Single pre-dose ECG extraction prior to dosing on Day 14.
7. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests.
8. Total Bile Acids (TBA) and PT/PTT required on Day -1, Day 2, Day 7, Day 14 and Day 21 only.
9. Lipid Panel required on Day -1, Day 7, Day 14 and Day 21 only.
10. See Section 8.2.5. Serum or urine pregnancy testing to be performed within 24 hours of dosing on Day 1.
11. In Part 2, VH4011499 will be administered as a PiB.
12. See Section 8.4. Blood samples drawn Day 15 and onward should be collected on an approximately 24-hour cycle (i.e., 24 hours post dose, 48 hours post dose, 72 hours post dose, etc).
13. At pre-dose, 0.5 h, 1 h, 2 h, 4 h, 6h, 8 h, 10 h and 12h. Plasma sample (pharmacokinetics) collection time points may be optimized based on emerging data from SAD.
14. At pre-dose only.
15. On Day 1 a urine sample will be collected pre-dose (40 mL) within 1 h prior to dosing and from time 0 up to 24 h post dosing. On Day 14 urine will be collected from time 0 to 24h post dosing. Details of urine collection and processing are detailed in the SRM.
16. The EnteroTracker will be swallowed 2.5 h post-dose. A small food cue will be provided at 5.25 post dose and the string will be removed at 6.5 h post dose. Details of bile collection and processing are detailed in the SRM. See Section 8.4for further detail.

Table 5 Part 2 MAD - Outpatient Visit Days 28, 35 and 42

Procedure	Day		
	28	35	42[5]
Visit Window	±1 day	±1 day	±1 day
Brief Physical Exam[1]	X	X	X
Vital signs	X	X	X
12-lead ECG[2]	X	X	X
Clinical Laboratory Test[3]	X	X	X
Pregnancy Test[4]	X	X	X
Plasma sample (pharmacokinetics)	X	X	X
Adverse Event Review	<==========		==========>
Concomitant Medication Review	<==========		==========>

1. See Section 8.2.1 Brief physical exams may be made full physical exams at the discretion of the investigator. Weight will be measured on Day 42.
2. See Section 8.2.3 for details of 12-lead ECGs.
3. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests. Total Bile Acids, PT/PTT and Lipid Panel required in each weekly clinical laboratory test.
4. See Section 8.2.5. Serum or urine pregnancy testing to be performed.
5. In the event terminal half-life is longer than predicted, PK and laboratory assessment will occur every 7 days until an estimated 5 half-lives have elapsed.

Table 6 Part 2 MAD/Drug-Drug Interaction (DDI) - Inpatient Days -1 to 22

Procedure	Day																						
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Admission to Unit	X[1]																						
Discharge from Unit																							X
Drug/alcohol/cotinine screen	X																						
SARS-CoV-2 PCR Test[1]	X[1]	X[1]						X							X								X
Brief Physical Exam[2]	X							X								X							X
Vital Signs	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X	X	X	X	X	X
12-lead ECG[4]	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]	X		X		X	X	X
Meals		*See Section* 5.3.1																					
Clinical Laboratory Test[6,7,8]	X			X			X		X				X			X							X
Pregnancy Test[9]		X																					
Randomization		X																					
Drug Administration[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Midazolam Administration[11]		X	X													X							
Pulse oximetry[12]		X	X													X							
Plasma Sample (VH4011499 Pharmacokinetics)[13]			X[14]	X[15]	X[15]	X[15]	X[15]		X[15]		X[15]		X[15]	X[15]	X[15]	X[14]	X	X	X	X	X	X	X
Plasma Sample (VH4011499 metabolism)[13]			X[14]	X[15]												X[14]	X						
Plasma Sample (Midazolam and 1-hydroxymidazolam Pharmacokinetics)[16]		X	X	X												X	X						
Plasma Sample (coproporphyrin I)[17]		X	X													X	X						

Procedure	Day																						
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Urine Sample (VH4011499 metabolism)[18]			<=====>													<=====>							
Bile Sample (EnteroTracker)[19]															X								
Adverse Event Review	<===>																						
Concomitant Medication Review	<===>																						

1. Two consecutive SARS-CoV-2 PCR negative results are required prior to dosing. The tests should be performed on different days with the first test performed between Day -7 and Day -1 and the second test performed pre-dose. Admission to unit may be done on Day -2 if necessary for SARS-CoV-2 PCR testing.
2. See Section 8.2.1 for details of brief physical examination. Brief physical exams may be made full physical exams at the discretion of the investigator.
3. Pre-dose and 1h, 3h, 6h and 12h. All vitals should be measured pre-dose; only blood pressure and pulse rate are measured for all remaining daily timepoints.
4. See Section 8.2.3 for details of 12-lead ECGs and cardiodynamic assessment (Holter monitoring).
5. Pre-dose triplicate ECG required on Day 1 within 90 minutes of dosing. Dose administration day ECGs will be collected pre-dose and 3, 6, 9 and 12-hours post-dose.
6. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests.
7. Total Bile Acids (TBA) and PT/PTT required on Day -1, Day 3, Day 8, Day 15 and Day 22 only.
8. Lipid Panel required on Day -1, Day 8, Day 15 and Day 22 only.
9. See Section 8.2.5. Serum or urine pregnancy testing to be performed within 24 hours of dosing on Day 1.
10. In Part 2, VH4011499 will be administered as a PiB.
11. Midazolam will be co-administered with VH4011499 on Day 2 and Day 15.
12. Continuous pulse oximetry monitoring will begin within 15 minutes of dosing with midazolam and will continue until 6 hours post midazolam dosing. Pulse oximetry will be recorded pre-dose and 0.25, 0.75, 1, 2, 3, 4, 5 and 6 h post dose.
13. See Section 8.4. Blood samples drawn Day 15 and onward should be collected on an approximately 24-hour cycle (i.e., 24 hours post dose, 48 hours post dose, 72 hours post dose, etc).
14. pre-dose, 0.5 h, 1 h, 2 h, 4 h, 6h, 8 h, 10 h and 12h. Plasma sample (pharmacokinetics) collection time points may be optimized based on emerging data from SAD.
15. At pre-dose only.
16. Plasma PK samples for midazolam and 1-hydroxymidazolam will be collected pre-dose (within 15 mins prior to dosing) and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12h, and 24h post midazolam dose on Day 1 and Day 15. On Day 2, plasma PK samples for midazolam and 1-hydroxymidazolam will be collected 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12h, and 24h post midazolam dose. The 24 h post Day 1 dose collection will be pre-dose on Day 2.
17. Plasma PK samples for coproporphyrin I will be collected pre-dose of midazolam (within 15 mins prior to dosing) and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12h, and 24h post midazolam dose on Day 1 and Day 15.
18. On Day 2 a urine sample will be collected pre-dose (40 mL) within 1 h prior to dosing and from time 0 up to 24 h post dosing. On Day 15 urine will be collected from time 0 to 24h post dosing. Details of urine collection and processing are detailed in the SRM.
19. The EnteroTracker will be swallowed 2.5 h post-dose. A small food cue will be provided at 5.25 post dose and the string will be removed at 6.5 h post dose. Details of bile collection and processing are detailed in the SRM. See Section 8.4 for further details.

Table 7 Part 2 MAD/ DDI - Outpatient Visit Days 28, 35 and 42

Procedure	Day		
	28	35	42[5]
Visit Window	±1 day	±1 day	±1 day
Brief Physical Exam[1]	X	X	X
Vital signs	X	X	X
12-lead ECG[2]	X	X	X
Clinical Laboratory Test[3]	X	X	X
Pregnancy Test[4]	X	X	X
Plasma sample (VH4011499 pharmacokinetics)	X	X	X
Adverse Event Review	<==========>		
Concomitant Medication Review	<==========>		

1. See Section 8.2.1 Brief physical exams may be made full physical exams at the discretion of the investigator. Weight will be measured on Day 42.
2. See Section 8.2.3 for details of 12-lead ECGs.
3. See Appendix 2: Clinical Laboratory Tests Clinical Laboratory Tests for details of Clinical Laboratory Tests. Total Bile Acids, PT/PTT and Lipid Panel required in each weekly clinical laboratory test.
4. See Section 8.2.5. Serum or urine pregnancy testing to be performed.
5. In the event terminal half-life is longer than predicted, PK and laboratory assessment will occur every 7 days until an estimated 5 half-lives have elapsed.

Table 8 Part 3 Tablet PK - Inpatient Days -1 to 7

Procedure	Day																		
	Day -1	Day 1												2	3	4	5	6	7
		Pre-dose	0 h	0.5h	1 h	1.5 h	2h	3 h	4h	6 h	8h	10h	12h	24h	48h	72h	96h	120h	144h
Admission to Unit	X[9]																		
Discharge from Unit																			X
Drug/alcohol/cotinine screen	X																		
Brief Physical Exam[1]	X													X					X
Vital signs[2]	X	X			X		X		X		X		X	X	X	X	X	X	X
12-lead ECG[3]	X	X[4]			X				X				X	X	X		X		X
Meals		X		See Section 5.3.1															
Clinical Laboratory Tests[5,6,7]	X													X	X	X	X	X	X
SARS-CoV-2 PCR Test[8]	X[8]	X[8]																	X
Pregnancy Test[9]		X																	
Randomization		X																	
Drug administration[10]			X																
Plasma Sample (pharmacokinetics)[11]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Day																	
	Day -1	Day 1												2	3	4	5	6	7
		Pre-dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	48 h	72 h	96 h	120h	144h
Adverse Event Review	<==========>																		
Concomitant Medication Review	<==========>																		

1. Brief physical exams may be made full physical exams at the discretion of the investigator.
2. Day 1 measured pre-dose; only blood pressure and pulse rate are measured for all remaining Day 1 timepoints.
3. See Section 8.2.3 for details of 12-lead ECGs.
4. At pre-dose a triplicate 12-lead ECG is required within 90 minutes of dosing.
5. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests.
6. Total Bile Acids (TBA) and Coagulation Panel required on Day -1, Day 2 and Day 7 only.
7. Lipid Panel required on Day -1 and Day 7 only.
8. Two consecutive SARS-CoV-2 PCR negative results are required prior to dosing. The tests should be performed on different days with the first test performed between Day - 7 and Day -1 and the second test performed pre-dose. Admission to unit may be done on Day -2 if necessary for SARS-CoV-2 PCR testing.
9. See Section 8.2.5. Serum or urine pregnancy testing to be performed within 24 hours of dosing on Day 1.
10. In Part 3, VH4011499 will be administered as a tablet.
11. PK blood samples drawn post-dose should be collected on an approximately 24-hour cycle (i.e., 24 hours post last dose, 48 hours post last dose, 72 hours post last dose, etc).

Table 9 Part 3 Tablet PK - Outpatient Visit Days 14, 21 and 28

Procedure	Day		
	14	21	28[8]
Visit Window	±1 day	±1 day	±1 day
Brief Physical Exam[1]	X	X	X
Vital signs[2]	X	X	X
12-lead ECG[3]	X	X	X
Clinical Laboratory Test[4,5]	X	X	X
Pregnancy Test[6]	X	X	X
Plasma sample (pharmacokinetics)[7]	X	X	X
Adverse Event Review	<==========		==========>
Concomitant Medication Review	<==========		==========>

1. See Section 8.2.1 for details of brief physical exam. Brief physical exams may be made full physical exams at the discretion of the investigator. Weight will be measured on Day 28.
2. See Section 8.2.2 for details of Vital Sign measurements.
3. See Section 8.2.3 for details of 12-lead ECGs.
4. See Appendix 2: Clinical Laboratory Tests for details of Clinical Laboratory Tests.
5. Total Bile Acids, Coagulation Panel and Lipid Panel to be included in each weekly clinical laboratory test.
6. See Section 8.2.5. Serum or urine pregnancy testing to be performed.
7. See Section 8.4 for further details for plasma PK sample collection. One whole blood sample of sufficient volume will be processed to measure concentrations of VH4011499.
8. In the event terminal half-life is longer than predicted, PK and laboratory assessment will occur every 7 days until an estimated 5 half-lives have elapsed.

2. INTRODUCTION

VH4011499 (also referred to as GSK4011499) belongs to a novel class of ARV agents targeting a highly conserved region of the HIV-1 capsid protein.
Investigational VH4011499 is being developed for people living with HIV-1 to be part of a long-acting ARV treatment regimen. The purpose of this FTIH study with VH4011499 (via powder-in-bottle) is to initially characterize the tolerability, safety, and pharmacokinetics of VH4011499. The drug concentrations obtained from oral administration of VH4011499 in both the single ascending dose and repeat ascending dose parts of this study will help inform subsequent development of long-acting VH4011499.

2.1. Study Rationale

This is a double-blind, randomized, placebo-controlled, FTIH study in a combined single-ascending (Part 1) and multiple-ascending (Part 2) dose design to assess the tolerability, safety and pharmacokinetics of orally administered VH4011499 in healthy participants. This study is designed to evaluate: the safety, tolerability, and PK properties of VH4011499 when administered as single and multiple ascending dosing with the PiB formulation; the safety, tolerability and PK properties of the VH4011499 tablet formulation; and any effect of VH4011499 on the activity of CYP3A using midazolam as a probe and on OATP1B1/1B3 using an endogenous biomarker as a probe (coproporphyrin I). The data gathered in this study will inform further evaluation of VH4011499 in people living with HIV-1 CCI [redacted]

2.2. Background

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 an opportunity for developing more conveniently dosed and better tolerated ARV regimens. Long-acting injectable versions of drugs are being developed to improve convenience by extending the dosing interval from every day to every month or longer. These therapeutic options hold great promise for future treatment and represent an emerging paradigm for the treatment and prevention of HIV-1 infection. An all long-acting ARV regimen that is dosed every month or longer offers many potential advantages over daily dosed regimens, including: improved ARV adherence, improved treatment satisfaction, and minimizing the patient's daily reminder of their HIV status.

VH4011499 belongs to a novel class of ARV agents targeting a highly conserved region of the HIV-1 capsid protein. In-vitro experiments suggest its primary antiviral mechanism of action is derived from inhibition of a replication step early in the viral replication cycle prior to integration of the HIV-1 provirus into the host cell chromatin. VH4011499 also possesses a less potent late antiviral activity, reducing production of infectious virions from virus-producing cells [GSK Document Number RPS-CLIN-026329]. Of note,

VH4011499 is ViiV's second capsid inhibitor in clinical development and is preceded by VH4004280 which is currently in Phase 1 [ViiV Healthcare Protocol for Study 217058, 2022].
There are currently no capsid inhibitors approved for the treatment of HIV infection, although clinical efficacy and a generally favorable safety profile has been demonstrated in an investigational capsid inhibitor currently in development [Gupta, 2022; Oguagu, 2022]. In cell culture, VH4011499 exhibited potent antiviral activity against a wide spectrum of HIV-1 isolates and subtypes and also demonstrated no cross-resistance with currently approved ARV classes [GSK Document Number RPS-CLIN- 026329]. The potential to develop VH4011499 as a long-acting medicine is further supported by nonclinical studies (including rat and dog studies up to 28 days) that show a favorable toxicity, safety and pharmacokinetic profile for VH4011499 [GSK Document Number RPS-CLIN-026329].

A detailed description of the non-clinical pharmacology, pharmacokinetics, toxicology, virology, and the chemistry and manufacturing of VH4011499 is provided in the Clinical Investigator's Brochure [GSK Document Number RPS-CLIN-026329].

2.3. Benefit/Risk Assessment

In the definitive (GLP) 28-day repeat dose oral studies in rats and dogs with VH4011499 CCI [redacted], increases in liver enzymes (up to 11.3-fold pre-treatment levels at a mean CCI [redacted]) were observed in dogs at the highest dose tested, which was also considered the NOAEL in this study. There were no histologic correlates in the liver and no changes in liver weight in the dogs, and no adverse findings in the definitive rat study up to the highest dose and NOAEL of CCI [redacted]. There were no significant findings in GLP non-clinical studies conducted to assess genotoxicity, safety pharmacology and phototoxicity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VH4011499 may be found in the Clinical Investigator's Brochure [GSK Document Number RPS-CLIN-026329].

Midazolam Probe (Part 2, MAD/DDI dosing group(s)): Based on in vitro data, there is potential for inhibition of CYP3A by VH4011499 leading to increased midazolam exposures and a deeper and more prolonged CNS suppression. There is also potential for induction of CYP3A by VH4011499 leading to decreased midazolam exposures. To allow for accurate assessment of PK as a result of either CYP3A inhibition or induction while minimizing the risk of serious CNS suppression, a 5 mg oral dose of midazolam has been selected for this study. Of note, many drug interaction studies with potent CYP3A inhibitors (e.g., azole antifungals including ketoconazole) have been conducted with midazolam doses as high as 15 mg [Backman 1998; Olkkola, 1994]. Though some of these studies have reported deeper or longer sedation, no serious adverse events have been reported. Additionally, during dosing with midazolam in the present study, close observation for signs of CNS suppression as well as pulse oxygenation monitoring and timed respiratory rate will be implemented, and flumazenil will be readily available. [Rogers 2022].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug(s) VH4011499		
Drug-induced liver injury and/or clinically significant liver chemistry elevations	**VH4011499:** In vitro, VH4011499 CCI [redacted] In the definitive 28-day repeat dose dog study with VH4011499, at the CCI [redacted] there were increases relative to predose 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 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 (CCI [redacted]), there were no adverse effects of VH4011499, including no increases in liver enzymes, total bile acids or bilirubin. **VH4004280:** In vitro, VH4004280 CCI [redacted]. In the definitive 28 day repeat dose dog study, minimally increased mean liver weights and increased total bile acids (1 animal) were seen at CCI [redacted], however these were not associated with any microscopic liver findings. In the 28 day repeat dose rat study, 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	Participants with current or history of liver disease, history of or current infection with HBV or HCV or known hepatic or biliary abnormalities are excluded from participation in this study (see Exclusion Criteria, Section 5.2). Participants will be closely monitored for liver related AE and laboratory abnormalities, including serum total bile acids. Sentinel dosing is included (see Section 4.1). Liver chemistry participant stopping criteria are defined (see Section 7.1.1.).

	hepatobiliary injury, they were of low magnitude and without correlating histopathological findings.	
Increases in cholesterol and triglycerides	**VH4011499:** No increases in cholesterol or triglycerides and no macroscopic or microscopic findings in the liver were observed in the definitive 28 day repeat dose toxicity studies in dog and rat with VH4001499. **VH4004280:** In the definitive 28 day 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.	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.
Increases in WBC and activated PTT	**VH4011499:** No increases in WBC or PTT were observed in the definitive 28 day repeat dose toxicity studies in dog and rat with VH4001499. **VH4004280:** In the 28-day definitive dog study (CCI [redacted]) with VH4004280, increases in neutrophils and monocyte counts were observed, together with an increase in activated partial thromboplastin time.	Participants will be closely monitored for relevant AEs and laboratory abnormalities. Hematology Panel and Coagulation Panel are included in routine clinical laboratory tests as detailed in the SoA. Sentinel dosing is included (see Section 4.1). See Section 7.4.2 for clinical stopping criteria applicable to this potential risk.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug(s) VH4011499		
Drug Interactions (inhibition of OATP1B1/1B3)	In vitro, VH4011499 is a OAT1B1/1B3 inhibitor. The potential clinical impact will be investigated in this study using the biomarker coproporphyrin.	Co-medications, including OATP1B1/1B3 substrates, are prohibited in FTIH.
Drug Interactions (inhibition and induction of CYP3A4)	In vitro, VH4011499 is a CYP3A4 inducer and a CYP3A4 inhibitor. The potential clinical impact will be investigated in this study using midazolam as a probe substrate for CYP3A4. Midazolam may cause respiratory depression and transient drowsiness.	Co-medications, including CYP3A4 substrates, are prohibited in FTIH.
Midazolam		
Respiratory depression and transient drowsiness	Midazolam may cause respiratory depression and transient drowsiness.	Screening: Eligible participants will be overtly healthy as determined by a medical professional based on medical evaluation. On Treatment: Participants will be housed throughout study conduct to ensure rapid diagnosis and management of any potential event. To monitor for the respiratory effects of midazolam, continuous pulse oximetry and timed respiratory rate will be measured on probe substrate drug dosing days (See SoA,

		Section 1.3) To allow for accurate assessment of PK as a result of either CYP3A inhibition or induction while minimizing the risk of serious CNS suppression, a 5mg oral dose of midazolam has been selected for this study.

2.3.2. Benefit Assessment

This is a study in healthy participants and as such there is no expected benefit to administration of VH4011499. Participation in this study may contribute to the process of developing new therapies for HIV. There may be benefit to individual participants from the medical evaluations and assessments that could identify conditions that the participant was previously unaware.

2.3.3. Overall Benefit: Risk Conclusion

In non-clinical oral studies, increases in liver enzymes were observed, which were not accompanied by macroscopic or microscopic findings or weight changes in the liver. The increased liver enzymes in animals was observed at systemic exposures that were 244-692 times higher than the predicted clinical efficacious AUC(0-24) and Cmax. The protocol will exclude participants from the study with any pre-existing liver disease and all participants will be closely monitored for liver related AEs and laboratory abnormalities, with additional monitoring of total bile acids and lipids.

In addition, consistent with Sponsor guidance for early phase studies, this study will be conducted in one or more clinical research units with prior experience conducting first-time-in-human-trials, sufficient overnight facilities and immediate emergency care capabilities. Moreover, part 1 (SAD) must be conducted in a hospital based/adjacent inpatient clinical trial unit

ViiV Healthcare has assessed this study for any risks that may be posed to participants taking part. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of FDA and EMEA guidance on strategies to identify and mitigate risks for FTIH clinical trials with investigational medicinal products.

More detailed information about the known and expected benefits and risks of VH4011499 can be found in the Clinical Investigator's Brochure [GSK Document Number RPS-CLIN-026329].

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single (Parts 1 and 3) and multiple (Part 2) doses of VH4011499 in healthy participants.	• Incidence of adverse events (AEs), severity of AEs and proportion of participants who discontinue treatment due to AEs • Absolute values, change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters [consisting of total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)]
To describe the plasma PK characteristics of VH4011499 in healthy participants following single (Part 1) and multiple (Part 2) doses.	• Area under the plasma-concentration time curve (AUC): AUC0-inf for single dose and AUC(0-t) for repeat dose. • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life (t1/2) will be calculated for each part (Part 1 SAD, and Part 2 MAD) as data in each part permits.
Safety	
To further assess the safety and tolerability of single (Parts 1 and 3) and multiple (Part 2) doses of VH4011499 in healthy participants.	• Post baseline values and changes over time of vital signs and ECG parameters • Absolute values, change from baseline and maximum toxicity grade increase from baseline for hematology, coagulation and remaining chemistry panels
CCI [redacted]	

CCI

3.1. Estimands

3.1.1. Primary Safety Estimands

The primary Safety estimands aim to assess the proportion of participants with Adverse Events (including severity), proportion of participants with AEs leading to discontinuation of study treatment and provide summaries of absolute values and change from Baseline in liver panel laboratory parameters as well as maximum toxicity grade increase from Baseline in healthy volunteers receiving VH4011499 or placebo.

The primary Safety estimands are described by the following attributes:

Population	Safety analysis set
Treatment	Part 1: single oral dose of VH4011499 PiB or placebo Part 2: multiple oral doses (once daily) of VH4011499 or placebo, with a midazolam probe administered on Day 1, Day 2, and Day 15 in DDI dosing group(s) Part 3: single oral dose of VH4011499 tablet
ICEs	Discontinuation of study treatment due to any reason, will be addressed with treatment policy strategy in Part 2 (discontinuation of study treatment can't occur in Parts 1 or 3 as participants will receive only 1 dose). The occurrence of the ICE is considered irrelevant in defining the treatment effect of interest. All safety data will be included in the analysis up to the end of the follow-up period irrespective of the occurrence of this ICE.
Endpoints	• Incidence and severity of AEs • Incidence of AEs leading to discontinuation of study treatment • Absolute values and change from Baseline in liver panel laboratory parameters • Liver panel laboratory parameters maximum grade increase post-Baseline relative to Baseline
Summary Measure	• Number and percentage in each treatment arm (i.e., VH4011499 for each dosing group or placebo collectively from all dosing groups) for AEs and AEs leading to study treatment withdrawal • Summaries (e.g., mean, median, std etc.) of absolute values and change from Baseline values by visit and treatment arm (i.e., VH4011499 for each dosing group or placebo collectively from all dosing groups) in liver panel laboratory parameters. • Number and percentage of participants with maximum grade increase relative to Baseline in liver panel laboratory • parameters by treatment arm.

Rationale for primary Safety estimands:

This attempts to estimate safety effects likely to be attributable to the drug irrespective of whether the participant completed the treatment. Further details of the analyses of primary safety endpoints will be provided in the SAP.

3.1.2. Primary Pharmacokinetic Estimand

The primary Pharmacokinetic estimand aims to assess summary statistics (e.g. geometric mean, median, %CV etc.) of PK parameters in healthy participants following a single oral dose of VH4011499 PiB in Part 1 and multiple oral doses (once daily) of VH4011499 in

Part 2, while on and post treatment and in the absence of intake of non-permitted concomitant medication (see Section 6.8).

The primary Pharmacokinetic estimand is described by the following attributes:

Population	VH499 Pharmacokinetic analysis set
Treatment	Part 1: single oral dose of VH4011499 PiB Part 2: multiple oral doses (once daily) of VH4011499 with a midazolam probe administered on Day 1, Day 2, and Day 15 in DDI dosing group(s)
ICEs	Study treatment discontinuation in part 2 will be addressed with while on-treatment strategy. Further details will be provided in the SAP.
Endpoints	• Part 1: AUC(0-inf), Cmax, tmax, t1/2 • Part 2: AUC(0-τ), Cmax, tmax, t1/2 at Day 14 (for dosing groups without midazolam administration) or at Day 15 (for dosing groups with midazolam administration)
Summary Measure	• Summary statistics (e.g. geometric mean, geometric %CV, arithmetic mean, median, std, min, max etc.) by dosing group

Rationale for primary PK estimand:

Discontinuation of study treatment may bias the evaluation of Pharmacokinetic behavior of study treatment. Further details of the analyses of primary Pharmacokinetic endpoints will be provided in the SAP.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, 3-Part, double-blind (sponsor unblinded), randomized, placebo-controlled, single and multiple-ascending-dose study in healthy participants. The purpose of this study is to evaluate: the safety, tolerability, and PK properties of VH4011499 when administered as single and multiple ascending dosing with the PiB; the safety, tolerability and PK properties of the VH4011499 tablet formulation; and any effect of VH4011499 on the activity of CYP3A using midazolam as a probe and on OATP1B1/1B3 using an endogenous biomarker as a probe (coproporphyrin I). Approximately 90 healthy participants are planned to be randomized, in Part 1 (SAD, n=48), Part 2 (MAD, n=36), and Part 3 (Tablet PK, n=6) from one or more centers in the US.

All dosing and 7 day post last-dose in clinic follow-up will be conducted in clinical trial units with experience in conducting first-time-in-human studies with sufficient overnight facilities and immediate emergency care capabilities. Moreover, Part 1 (SAD) must be conducted in a hospital based/adjacent inpatient clinical trial unit. A final follow up outpatient visit will take place approximately 28-days post final dose in Part 1 (SAD), Part 2 (MAD), and Part 3 (Tablet PK), as indicated in the Schedule of Activities (SoA), Section.1.3. The 28-day post final dose follow-up assumes a potential maximum half-life of 3-5 days for VH4011499. While the estimated half-life prior to starting the study is 13 hours, the actual half-life will be defined as data emerge from the study. The study is designed to ensure adequate PK follow-up for all participants. The follow-up duration may be altered if the actual half-life is significantly longer or shorter than predicted.

If actual PK parameters differ significantly from predicted values (e.g. if half-life is significantly longer or shorter than the predicted), then the duration of in clinic stay, duration of post last dose follow-up, determination of subsequent doses, dosing frequency and total duration of dosing may be altered. The duration of post dose follow-up is not intended to exceed five half-lives.

Part 1 (SAD) will investigate single doses of VH4011499 from the starting dose up to a maximum safe dose that provides adequate dose information for future dosing requirements in the VH4011499 development program and does not exceed the NOAEL.

A summary of overall study design for Parts 1 and 2, including proposed doses, sample size and order, is presented in Table 10 (Part 1 SAD) and Table 11 (Part 2 MAD).

4.1.1. Part 1 (SAD)

Part 1 (SAD) will be conducted in up to 6 separate dosing groups. Each participant will be randomized to receive a single dose of blinded VH4011499 or blinded PBO (in a 6:2, active:PBO ratio) administered orally. Details of the starting dose and dose escalation can be found in Section 4.3.2 and Section 4.3.5, respectively. Dose escalation decisions, including the determination of subsequent doses to be administered in Part 1, will be determined by the SDEC, see Section 10.1.5 but will be constrained by any emerging

safety or tolerability concerns and to a maximum 5x the predicted exposure increase between consecutive dosing groups (e.g., dosing group 2 and dosing group 3) where predicted VH4011499 concentrations would not exceed mean NOAEL criteria.

Table 10 Part 1 SAD

	Dosing Group	Predicted Dose[1] (mg)	CCI [redacted]
SAD (6 active:2 placebo)	1	25 mg	
	2	Dose Group 2	
	3	Dose Group 3	
	4	Dose Group 4	
	5 (optional expansion group)[3]	As required	
	6 (optional expansion group)[3]	As required	

1. Doses beyond group 1 will be decided by the SDEC based on emerging PK and safety data from prior dosing groups.
2. Calculated using the rat CCI [redacted] NOAEL dose. Target fold coverage can be revised based on emerging data.
3. Dosing groups 5 and 6 are optional expansion groups used to dose escalate up to a maximum dose whose predicted VH4011499 concentrations would not exceed mean NOAEL criteria or other predefined limits, to repeat a previous dose level, or to dose de-escalate.

At the start of each SAD dosing group, 2 of the total number of participants will serve as sentinel participants, with one receiving blinded VH4011499 and the other receiving blinded PBO. The investigator may stagger dose administration time as needed for sentinel participants. Sentinel participants will be followed clinically for 24 hours following dose administration to monitor for emergence of adverse events. Following this period, if there are no safety concerns, in the judgement of the PI, on review of 24-hour safety data (including but not limited to vital signs, ECGs, available laboratory tests and adverse events) for sentinel participants, the remaining 6 participants will be subsequently dosed with blinded VH4011499 or blinded PBO, according to the randomization schedule. The PI may stagger dose administration time for remaining dosing group participants as needed. The 24-hour clinical observation period for sentinel participants and dose administration in subsequent participants may be reduced following completion of dosing group 1, if there are no safety or tolerability concerns.

The proposed dosing schedule is designed to investigate single doses of VH4011499 in Part 1 and then, at a suitable cross-over point, begin repeated once-daily dosing of VH4011499 in Part 2.

4.1.2. Part 2 (MAD)

Part 2 (MAD) will be conducted in up to 4 ascending repeat-dose groups. Each

participant will be randomized to receive a QD dose of blinded VH4011499 or blinded PBO administered orally for 14 days. Participants in non-DDI MAD dosing groups will receive daily doses of VH4011499 or PBO (6:2) on Day 1 through Day 14. In up to two dosing groups in Part 2 (MAD/DDI dosing group(s)), participants will receive a single dose of midazolam on Days 1, 2, and 15, and daily doses of VH4011499 or PBO (8:2) on Day 2 through to Day 15. A single dose of midazolam will be co-administered with a dose of VH4011499 or PBO on Days 2 and 15. The MAD/DDI dosing group(s) will also include the collection of endogenous biomarker (coproporphyrin I) samples before and following repeat dose administration of VH4011499 or PBO to investigate the potential of VH4011499 to inhibit OATP1B1/1B3. Review of available data from previous SAD and emerging MAD dosing groups will determine if the DDI potential of VH4011499 will be evaluated in one or two MAD dosing groups.

The starting dose in Part 2 (MAD) will be identified after preliminary PK data are evaluated in Part 1 (SAD).

For both Parts 1 and 2, doses will be escalated such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma Cmax and AUC observed at the NOAEL exposures defined in Section 4.3.3. See Section 4.3 for further details on dose predictions.

Table 11 Part 2 MAD

	Dosing Group	Predicted Dose[2]
MAD (6 or 8 active: 2 placebo)[1] Once daily (QD) dose for 14 days[2]	**1**	> anticipated therapeutic dose
	2	Up to maximum NOAEL exposure and not exceeding the permitted top dose
	3	
	4 (Optional expansion group)[3]	As required

1. Dosing groups requiring midazolam dosing to evaluate the DDI potential of VH4011499 will enroll 10 participants (8 active: 2 placebo). All other dosing groups will enroll 8 participants (6 active: 2 placebo).
2. Actual doses will be decided based on emerging PK and safety data from prior dosing groups in Part 1 and Part 2.
3. Dosing Groups 3 and 4 are optional expansion groups used to dose escalate of up to a maximum dose (whose predicted VH4011499 concentrations would not exceed the permitted top dose based on emerging data and safety cover), to repeat a previous dose level, or to dose de-escalate.

Details of the starting dose and dose escalation can be found in Section 4.3.6. Dose escalation decisions, including the determination of subsequent doses, dosing frequency and total duration of dosing to be administered in Part 2, will be determined by the SDEC (see Section 10.1.5).

4.1.3. Part 3 (Tablet PK)

Part 3 (Tablet PK) is an open-label, single-dose design to evaluate the safety, tolerability and PK properties of the tablet formulation of VH4011499, in comparison with existing data from VH4011499 PiB, in one dosing group of 6 participants. All participants will receive a single dose of the VH4011499 tablet on Day 1 and will remain in the clinic until completion of the Day 7 procedures. They will return to the clinic on Days 14 and 21 for follow up procedures and a final follow up visit on Day 28.

Details of the VH4011499 tablet dose can be found in Section 4.3.7. While there is only one dosing group in Part 3, the study will utilize a SDEC for instream review of emerging PK and safety data.

4.1.4. Screening, Follow-up & Study Participation Duration

Participants in all parts of the study will have a screening visit within 30 days prior to their first dose and a final follow up visit approximately 28-days following final dose in Part 1 (SAD), Part 2 (MAD), and Part 3 (Tablet PK). Duration of study participation

(from the Screening Visit to the final post-dosing Follow-up Visit) will be approximately 8 weeks for participants in Part 1 (SAD) and Part 3 (Tablet PK), and approximately 10 weeks for participants in Part 2 (MAD)

Duration of study participation may change, if actual PK parameters differ significantly from the predicted base case values (e.g., if half-life is significantly longer or shorter than the predicted).

Participants will not be replaced if the reason for discontinuation from the study is due to a safety concern. If participants prematurely discontinue the study for non-safety reasons or intolerance to ingestion of the study drug (e.g., vomiting the solution shortly after ingestion and/or intentionally choosing to not ingest the full dose because of participant preference issues such as taste or smell), 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. 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.

4.2. Scientific Rationale for Study Design

This FTIH study, conducted in healthy adult participants, is designed to assess the safety, tolerability, and PK of an oral powder formulation of VH4011499, an investigational HIV-1 capsid inhibitor. The data gathered within this FTIH study will inform subsequent clinical trials, including a follow-on Phase 2a POC study in HIV-1-infected participants. Clinical development plans for the VH4011499 compound, include studies with parenterally administered (subcutaneous and intramuscular) versions of the molecule. C [redacted] CI Part 3 (Tablet PK) is planned to evaluate the VH4011499 tablet formulation for comparison with the existing VH4011499 PiB data and will inform subsequent clinical trials.

All doses of VH4011499 in this oral FTIH study will be administered in the fed state (see Section 5.3.1 for details of moderate fat/calorie meal) with dosing starting after 5 minutes of completing a standardized moderate fat/calorie meal, unless otherwise indicated.

In Part 2 of the study (MAD), doses will exceed the anticipated effective dose in a daily oral regimen in order to study exposures that may occur in future clinical studies with alternative routes, formulations and dosing durations. This will be done without exceeding the NOAEL established in non-clinical toxicology studies.

4.3. Justification for Dose

This section describes the analyses conducted to estimate human VH4011499 PK profile, and to predict starting, top and anticipated therapeutic doses required to maintain plasma concentrations at levels expected to produce pharmacologic activity in HIV-1 infected subjects.

4.3.1. Human Pharmacokinetics Prediction

The pharmacokinetics of VH4011499 in human was estimated using several approaches to determine a range of starting, therapeutic and top doses to achieve the objectives of this study. The methods utilized were allometry, PBPK, FDA guidance on maximum safe starting dose and the analysis of data from lenacapavir, a molecule in the clinic with the same pharmacology. These approaches were used to anticipate VH4011499 clinical PK and/or estimate a safe starting dose. The details of each method are described in the Human Prediction Report [GSK Document Number TMF-14580566].

4.3.2. Starting Dose Rationale in Part 1 (SAD)

The proposed starting dose was based on a range of approaches including the anticipated therapeutic dose predictions and MRSD assessments. Guidance for Industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. FDA/CDER, July 2005.

The NOAEL doses identified from the 28-day GLP rat and dog studies were CCI and CCI, respectively. The CCI based on the respective rat and dog NOAEL doses. A 10-fold safety factor on the HEDs yields an approximate MRSD of CCI.

The estimated starting doses using allometry and additional approaches are summarized in Table 12.

Table 12 Estimated starting dose using different approaches

Starting Dose Estimation Approach	Estimate
Allometry	CCI
PBPK[1]	
Existing clinical data	
MRSD	

[1]Dose from PBPK model are based on CCI

The resulting starting dose of VH4011499 in part 1 (SAD) is 25 mg. This reflects a mitigation of any potential safety risks (e.g., elevated liver chemistries) to the clinical study participants, since this is the first time that VH4011499 will be dosed in man and

safety outcomes are uncertain.

The predicted exposures (based on an allometric PK model) of the proposed starting dose of 25 mg for CCI [redacted] are shown in Table 13.

Table 13 Projected exposure for the single starting dose of CCI [redacted]

Dose (mg)	CCI [redacted]	Predicted PK Parameters Median (90%PI)			Safety Coverage		
		C_{max} (ng/ml)	C_{24} (ng/ml)	$AUC_{0\text{-}inf}$ (ng*h/ml)	Fold-Dose (mg/kg)[1]	Fold-C_{max}[2]	Fold-AUC[3]
25		CCI [redacted]					
25							

[1]Fold dose = NOAEL dose in Rat (CCI [redacted]) /Proposed Dose in human mg/kg
[2]Fold C_{max} = NOAEL C_{max} in rats (CCI [redacted])/ C_{max}
[3]Fold AUC = NOAEL $AUC_{(0\text{-}24)}$ in rats (CCI [redacted])/ $AUC_{0\text{-}inf}$

4.3.3. Top Dose Rationale

The top dose is defined as the highest dose where the predicted mean plasma exposures at that dose level (either SAD or MAD) approaches but does not exceed the mean NOAEL exposures (CCI [redacted]). For both Parts 1 and 2, the predicted mean plasma exposure at the top dose levels will not exceed the mean plasma Cmax and AUC observed at the NOAEL exposures.

The predicted top dose of CCI [redacted] administered as a single dose is estimated to provide a median plasma CCI [redacted] CCI [redacted]. And the top dose will be reviewed based on the emerging human PK data from the initial low dosing groups studied.

4.3.4. Anticipated Therapeutic Dose Rationale

Steady-state trough concentrations are typically the PK parameter of interest for efficacy for other antiretroviral classes such as protease inhibitors and integrase inhibitors. A therapeutic dose is proposed as where CCI [redacted]

Estimates of concentration at the end of a dosing interval at steady state (C_τ) from allometric scaling resulted in a dose range CCI [redacted]. This dose range is expected to CCI [redacted]. The PBPK and evaluation of existing clinical data used the same efficacy thresholds and the estimated doses are reported in Table 14 Using clinical LEN data as a relative benchmark, an equivalent VH4011499 maintenance dose is estimated to be CCI [redacted] based on the CCI [redacted].

Table 14 Estimated therapeutic dose using different approaches

Approach	Estimate
Allometry	CCI [redacted]
PBPK[1]	
Existing clinical data	

[1]Doses from PBPK model achieving efficacious threshold are based on CCI [redacted]

4.3.5. Planned Doses and Safety Coverage (Part 1)

Dose escalations in Part 1 (SAD) will be governed in real-time by PK and safety stopping criteria (see Section 7.4.1 and Section 7.4.2). Doses following the first dose will be curtailed by responses to any safety, tolerance or other data, and predicted not to exceed mean NOAEL, and within a maximum 5x exposure increase. De-escalation of a dose or repeat of a dose level is permitted, if needed.

Based on the assumptions described above and PK predictions made with the allometry model, possible dose escalations are illustrated below in Table 15. These dose elevations and maximum SAD dose will be revised based on emerging PK and safety data. The proposed number of cohorts for Part 1 (SAD) is 4 with a further 2 for possible expansions

Table 15 Comparison of predicted human pharmacokinetics and NOAEL pharmacokinetics in rats for SAD dosing (Part 1)

Model-predicted human doses		PK Parameters (Median Range) of Model-predicted human doses[2]				Safety Coverage (ratio of human and rat PK parameters)		
Dose[1] (mg)	Dose (mg/kg)	C_{max} (ng/mL)	C24 (ng/mL)	$AUC_{(0-24)}$ (ng*h/mL)	$AUC_{(0-inf)}$ (ng*h/mL)	Fold-Dose (mg/kg)[3]	Fold-C_{max} [4]	Fold-AUC[5]

25	CCI [redacted]
125	
600	
1200	
2000	

[1] Doses beyond group 1 will be decided by the Safety and Dose Escalation Committee based on emerging PK and safety data from prior dosing groups.
[2] Median range of the parameter were predicted CCI [redacted].
[3]Fold dose = NOAEL dose in Rat (CCI [redacted] /Proposed Dose in human mg/kg
[4]Fold C_{max} = NOAEL C_{max} in rats (CCI [redacted])/Predicted human C_{max}
[5]Fold AUC = NOAEL $AUC_{(0-24)}$ in rats (CCI [redacted])/Predicted Human $AUC_{(0-inf)}$

4.3.6. Repeat Dosing Plan (Part 2)

The planned dosing regimen for Part 2 is QD (24h dosing intervals) for 14 days, judged sufficient to evaluate accumulation, repeat dosing PK and be able to evaluate future steady state exposures.

Part 2 (MAD) will be conducted in up to 4 ascending repeat-dose groups and each escalation is expected to be within 3x exposure increase. The top dose is defined as the highest dose where the predicted mean plasma exposures at that dose level approaches but does not exceed the mean NOAEL exposures (CCI [redacted]).

Dose escalation in the MAD will be governed by both MAD PK and safety stopping criteria (see Section 7.4.1 and Section 7.4.2).

4.3.7. Tablet PK (Part 3) Dose Selection

In Part 3, the safety, tolerability and PK of the VH4011499 tablet formulation will be evaluated in comparison with existing data from VH4011499 PiB. A tablet dose will be determined as a reasonable representative dose for this assessment, based on review of available data from previous dosing groups in Parts 1(SAD) and 2 (MAD) and predicted clinical doses.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed the entire dosing period and post dosing follow-up period, including the final follow up visit, as detailed in the SoA (Section 1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

AGE
1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT
2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. 3. Two consecutive SARs-CoV-2 PCR negative results are required prior to dosing.

WEIGHT
4. Body weight > 50kg and body mass index (BMI) within the range 19-32kg/m^2 (inclusive).

SEX AND CONTRACEPTIVE/BARRIER REQUIREMENTS
5. Male or female of non-childbearing potential a. Male Participants: Male participants (male sex assigned at birth) are eligible to participate if they agree to the following during the study drug period and for a period of 118 days (28-day post dose follow-up period plus an additional 90-day spermatogenesis cycle) after the last dose of study drug: • Refrain from donating semen Plus either: • Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Agree to use a male condom and female partner of child-bearing potential to use an additional highly effective contraceptive method with a failure rate of <1%, with low user dependency or that are user dependent, as described in Appendix 4: Contraceptive and Barrier Guidance

b. Female Participants:

a. A female participant (female sex assigned at birth) is eligible to participate if:

- She is a WONCBP, as defined in Section 10.4 Contraception and Barrier Guidance, and is not pregnant, nor breastfeeding. There is no requirement for female study participants considered WONCBP to use a highly effective method of contraception since, to be eligible, they must be of nonchildbearing potential.

OR

- She is a woman of childbearing potential (WOCBP) as defined in Section 10.4 Contraception and Barrier Guidance, and is using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, [as described in Appendix 4: Contraceptive and Barrier Guidance] during the study intervention period and for at least 58 days (e.g., 28- day post dose follow-up period plus 30 days (a menstrual cycle) after the last dose of study intervention. Highly effective, low user-dependency (with a failure rate of <1% per year) are limited to intrauterine devices/systems or bilateral tubal occlusion ≥3 months prior to screening.
  - A WOCBP must have a negative highly sensitive pregnancy test (serum as required by local regulations) within 24 hours before the first dose of study intervention (with VH4011499 or midazolam depending on the dosing group) (see Section 8.2.5: Pregnancy Testing).
  - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5 Pregnancy Testing.
  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

INFORMED CONSENT
6. Capable of giving signed informed consent as described in Section 10 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, neurological or psychiatric disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study drug or interfering with the interpretation of data. The investigator may contact the Sponsor medical monitor to discuss the inclusion of participants who have a history of specific conditions that are not expected to interfere with their participation in the study.
2. Abnormal blood pressure as determined by the investigator.
3. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
4. Breast cancer within the past 10 years.
5. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
6. QT interval corrected for heart rate according to Fridericia's formula (QTcF) >450 msec.

PRIOR/CONCOMITANT THERAPY
7. Past or intended use of over-the-counter or prescription medication [including Cytochrome P450 enzyme inducers or inhibitors, vitamins, herbal and dietary supplements (including St. John's Wort)] within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing and for the duration of the study, unless in the opinion of the Investigator and Sponsor, the medication will not interfere with the study medications, procedures, or compromise participant safety. Specific medications listed in Section 6.8 may be allowed.
8. Live vaccine(s) within 1 month prior to screening or plans to receive such vaccines during the study.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
9. Exposure to more than 4 new investigational products within 12 months prior to the first dosing day. 10. Current enrollment or past participation in another investigational study in which an investigational intervention (e.g., drug, human blood product, monoclonal antibody, vaccine, invasive device) was administered within 1 month prior to screening or 5 half-lives (whichever is longer). This includes excluding a participant who has been exposed with 1 month prior to screening to an experimental drug, human blood product, monoclonal antibody, or vaccine (which does not have emergency, conditional, or standard market authorization) for SARS-CoV-2. Note: Consult with the Sponsor medical monitor if clarification is needed. 11. Participation in the study would result in loss of blood or blood products in excess of 500 mL over a 56-day period. 12. Previously dosed in this clinical study.

DIAGNOSTIC ASSESSMENTS
13. ALT >1.5xULN. A single repeat test is allowed within a single screening period to determine eligibility. 14. Total bilirubin >1.5xULN (isolated total bilirubin >1.5xULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%). A single repeat test is allowed within a single screening period to determine eligibility. 15. Estimated serum creatinine clearance (using Chronic Kidney Disease Epidemiology Collaboration equation) <60 mL/min. 16. History of or current infection with hepatitis B or hepatitis C. 17. 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) within 14 days of inpatient admission, or having contact with known COVID-19 positive person/s in the 14 days prior to inpatient admission. 18. Positive pre-study drug/alcohol screen. 19. Positive HIV antibody test. 20. Cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.

OTHER EXCLUSIONS
21. Regular alcohol consumption within 6 months prior to the study defined as: An average weekly intake of >14 units for males or >7 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 22. Regular use of known drugs of abuse. 23. Sensitivity to the study drug, or components thereof, midazolam (For Part 2, MAD/DDI dosing group(s)), excipients contained therein, benzodiazepines, or drug or other allergy that, in the opinion of the investigator or Sponsor medical monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study drug until after the final dose.

No water is allowed for 2 hours after dosing, with the exception of water consumed for dosing. Water is allowed ad libitum at all other times.

All doses of VH4011499 in Part 1 (SAD), Part 2 (MAD), and Part 3 (Tablet PK) will be administered in the fed state (moderate fat/calorie). Participants will fast for at least 8 hours prior to dosing and will start eating their standardized moderate fat meal 30 minutes prior to the start of dosing. Participants will consume their meal in up to 25 minutes (leaving at least 5 minutes between the end of the meal and the start of dosing). The standardized moderate fat meal will contain approximately 600 calories, 30% of which are from fat.

In Part 2 (MAD) (Day 13 or Day 14 only), participants will undergo biliary metabolism testing using the EnteroTracker for analysis of VH4011499 and its metabolites. Participants will receive a food cue to stimulate gall bladder emptying at approximately 5.25 hours post dose. Examples of the high fat food item include sausage sandwich or cream cheese [2 tablespoons] on a bagel. The EnteroTracker will be removed 6.5 hours post dose.

All other meals will be provided as per the sites own standards.

5.3.2. Caffeine, Alcohol, and Tobacco

During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for

24 hours before the start of dosing (with VH4011499 or midazolam depending on the dosing group) until 2 weeks after discharge from the inpatient unit. Participants also should abstain from ingesting caffeine-or xanthine-containing products 24 hours prior to all remaining outpatient study visits until the end of that visit.

Use of alcohol or tobacco products will not be allowed from screening until after the final follow-up 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 (e.g., watching television, reading).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

Any individual who meets eligibility criteria is permitted to rescreen.

With one exception, individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Participants previously deemed eligible during the screening period unable to attend within the allowable screening window due to COVID-19 may be rescreened.

5.5. Criteria for Temporarily Delaying

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The active investigational interventions used in this study are VH4011499 PiB and VH4011499 tablet.

6.1. Study Intervention(s) Administered

Table 16 Study intervention(s) Administered

Intervention on Label	VH4011499 PiB	Placebo PiB	VH4011499 Tablet	Midazolam
Dose Formulation	PiB for reconstitution with 50 mL of vehicle (0.5% w/v CCI [redacted]	50 mL of vehicle (0.5% w/v CCI [redacted]	VH4011499 tablet	Oral syrup
Unit Dose Strength(s)	Oral Suspension of VH4011499	Not Applicable	25 mg and 100 mg	2 mg/mL
Dosage Level(s)	Starting single dose of 25 mg, subsequent doses to be determined at dose escalation meetings.	To match active.	Dose to be determined following review of available data from Parts 1 and 2.	5mg
Route of Administration	Oral	Oral	Oral	Oral
Dosing Instruction	Each dose to be reconstituted with 50 mL vehicle followed by additional rinses with Sterile Water for Irrigation/ Injection	Each dose to be reconstituted with 50 mL vehicle followed by additional rinses with Sterile Water for Irrigation/ Injection	Tablet(s) to be taken with water (~240 mL). Dose with food [moderate fat/calorie meal]. Full dosing	Dosing instructions will be provided in the SRM.

Intervention on Label	VH4011499 PiB	Placebo PiB	VH4011499 Tablet	Midazolam
	Dose with food [moderate fat/calorie meal]. Full dosing instructions will be provided in the SRM.	Dose with food [moderate fat/calorie meal]. Full dosing instructions will be provided in the SRM.	instructions will be provided in the SRM.	
Use	Clinical investigation	Placebo control	Clinical investigation	Clinical investigation
Sourcing	VH4011499 Active Powder, CCI [redacted] are provided centrally by the sponsor Sterile Water for irrigation/ injection provided by the site.	CCI [redacted] are provided centrally by the sponsor Sterile Water for irrigation/ injection provided by the site.	Provided in bulk by the Sponsor.	Provided locally by the study site, subsidiary, or designee.
Packaging and Labelling	Study drug will be provided in amber glass bottle with child resistant caps. Each bottle will be covered to obscure the appearance of the study drug. Each bottle will be labelled as required per country requirement.	Study drug will be provided in amber glass bottle with child resistant caps. Each bottle will be covered to obscure the appearance of the study drug. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in bulk by Sponsor. The investigator will package in glass or high-density polyethylene bottles. Each bottle will be labelled as required per country requirement.	Clinical site purchased commercial product.

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 drug received and any discrepancies are reported and resolved before use of the study drug.
- Only participants enrolled in the study may receive study drug and only authorized site staff may supply, prepare, or administer study drug.
- All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study drug are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study drug is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Sponsor medical monitor and/or VH/GSK study contact. 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. Measures to Minimize Bias: Randomization and Blinding

All participants will be randomized, according to the randomization schedule generated prior to the study by the Biostatistics Department at GSK using validated internal software. Each participant in Part 1 and Part 2 will be dispensed blinded study drug, labelled with his/her unique randomization number, throughout the study. Each participant scheduled to receive study drug will receive a treatment allocation number when randomized.

Parts 1 and 2 will be partially blinded. The blinding strategy is structured to ensure that no one who is involved in the management of individual participants is unblinded to treatment at the participant level.

- Participants will be blinded to their treatment.
- Site staff will be blinded with the exception of the unblinded pharmacist who will prepare the study drug.
- The Sponsor will be blinded with the exception of the statistician and clinical pharmacologist who will have access to unblinded data. The Sponsor's unblinded

Clinical Research Associate, and in the event of a Quality Assurance audit, the auditor(s), will be allowed access to unblinded study drug records at the site to verify that randomization/dispensing has been done accurately. The Sponsor will present data at SDEC meetings in a fashion that preserves the blinding of individual participants. Other Sponsor staff will remain blinded unless unblinding becomes absolutely necessary.

The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor study team must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor study team must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

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

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

6.4. Study Intervention Compliance

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

Participants will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug 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 drug. Study site staff will examine each participant's mouth to ensure that the study drug was ingested.

6.5. Dose Modification

The decision to proceed to the next dose level of VH4011499 in both Part 1 (SAD) and Part 2 (MAD) will be made by the SDEC as outlined in the SDEC Charter, based on safety, tolerability and PK data obtained from the prior dose level(s).

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

This study will enrol healthy participants only, therefore, no additional treatment from the Sponsor, including treatment with VH4011499, will be provided after study completion.

6.7. Treatment of Overdose

ViiV Healthcare does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

- Contact the Sponsor medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities to the planned end of sampling (at least 21 days after the last dose) or until VH4011499 can no longer be detected systemically (if the follow-up monitoring is extended based on emerging data).
- Obtain a plasma sample for PK analysis immediately if requested by the Sponsor medical monitor (determined on a case-by-case basis). Additional PK samples over time may be requested.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor medical monitor, based on the clinical evaluation of the participant. No dose modifications are permitted without prior discussion and consent from the SDEC.

6.8. Concomitant Therapy

The drug-drug interaction potential of VH4011499 has been evaluated in a series of in vitro studies [GSK Document Number RPS-CLIN-026329]. As the clinical risk of significant drug-drug interactions with VH4011499 as a perpetrator or a victim is currently unknown, participants in this study must abstain from taking concomitant medications. To this end, participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study drug until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interact with VH4011499 and interfere with the study.

Permitted medication(s):

- Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study.
- In the event of irritation from ECG leads, up to 2.5% topical hydrocortisone may be

used at the discretion of the investigator

- Vaccination with an approved vaccine for SARS-CoV-2 prior to or during study participation (see SRM for detailed guidance on acceptable timing for vaccination)
- Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the Sponsor medical monitor.

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 reviewed with the Study Sponsor Medical Monitor. The following details should be recorded:

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study drug. If study drug is permanently discontinued, every attempt will be made to continue follow-up data collection for the participant, assuming that the participant continues to provide consent to participate in the study. In most cases, the SoA should continue to be followed for participants that have discontinued study drug. The investigator should discuss each specific case with the medical monitor and agree which post dose assessments will not be performed (e.g., intensive PK and ECGs on Day 14 or Day 15 and bile collection on Day 13 or Day 14 may become less informative and therefore not done). See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

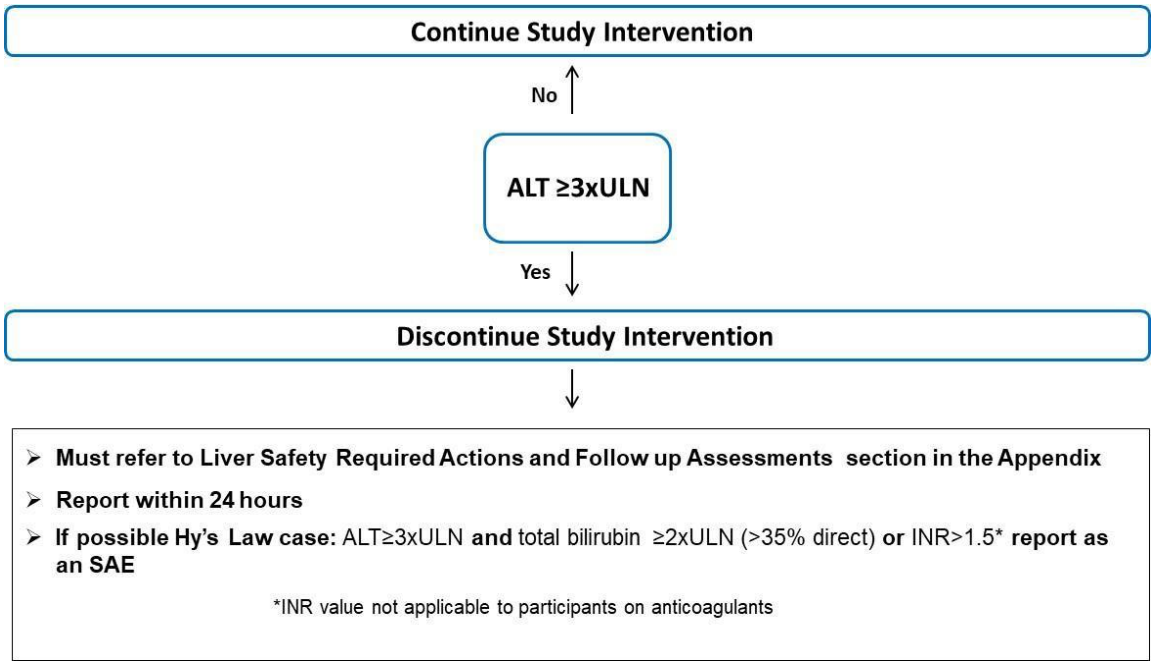
7.1.1. Liver Chemistry Stopping Criteria

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

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

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

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



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

Refer to Appendix 5: Liver Safety: Required Actions and Follow-up Assessments for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

A participant that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study drug. See Section 8.2.3.

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

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF ≤60 msec) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. SARS-COV-2 Stopping Criteria

A participant must be withdrawn from study drug and discontinued from the study if he/she is found to have SARS-CoV-2 infection during an inpatient stay. The management of all other inpatient participants within the same dosing group should be discussed by the investigator and the medical monitor. Individuals who have not been exposed to the virus will be permitted to remain in the clinic and fulfil their inpatient stay. Individuals

who have been exposed will be discharged home regardless of whether they are symptomatic. Individuals who are discharged home may still be able to continue in the study at the discretion of the investigator and the medical monitor assuming the participant adheres to current Centers for Disease Control and Prevention guidance for exposure and assuming the participant continues to have a negative SARS-CoV-2 test status. Participants who test positive during the outpatient phase of the trial 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.

7.1.4. Temporary Discontinuation

Temporary discontinuation of study drug for a study participant in this study is not allowed.

7.1.5. Rechallenge

Study treatment restart or rechallenge in this study is not allowed.

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

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

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

Participants will not be replaced if the reason for discontinuation from the study is due to a safety concern. If participants prematurely discontinue the study for non- safety reasons or intolerance to ingestion of the study drug (i.e., vomiting the solution shortly after ingestion), 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

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) for data to be collected at the time of study discontinuation.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4. Study Pausing and/or Stopping Criteria

7.4.1. PK Stopping Criteria for SAD and MAD

CCI

Assuming that safety stopping criteria have not been met (See Section 7.4.2) and the top

dose in MAD has not already been achieved (See Section 4.3.6), dose escalation in Part 2 (MAD) will be stopped in the event that safety or PK stopping criteria are not met, but the Bayesian predicted probability is >50% that any participant's C_{max} or AUC_{0-24} on the day of the last dose in the subsequent dose will exceed the MAD PK stopping criteria. At the time of any dose escalation decision, the most current NOAEL parameters for VH4011499 (which are based on emerging non-clinical toxicity data and defined in the SDEC charter) will be used and will not be exceeded.

7.4.2. Clinical Criteria for Pausing and/or Stopping the Study

Cumulative safety parameters and all available pharmacokinetic parameters from previous dosing cohorts will be fully assessed by the SDEC before selecting the subsequent dose to be used within the next dosing cohort in Parts 1 and 2. Any trends toward drug-related laboratory changes or other safety events will be fully evaluated. The decision to dose- escalate will be based on the nature, severity, and frequency of any safety and/or tolerability observations. The decision to dose-escalate may be delayed to allow the collection of additional safety data, if clinically indicated. While there is only one dosing group in Part 3, the study will utilize the SDEC for instream review of emerging data. All available safety parameters and pharmacokinetic parameters through at least Day 7 will be fully assessed by the SDEC and any trends toward drug-related laboratory changes or other safety events will be fully evaluated.

If the following number of participants, within the ongoing cohort of active participants, develops clinically significant changes in safety parameters or significant AEs thought to be drug related, the dose escalation will be paused until all of the cumulative safety data are reviewed by the SDEC and the VSLC. The VSLC is comprised of senior representatives from various departments, including clinical development, toxicology, pharmacovigilance, epidemiology, and medical affairs.

- Death of one participant, regardless of causality assessment.
- One participant experiences a Grade 4 AE or an SAE (of any grade) that the Investigator considers reasonably attributable to VH4011499.
- Two participants (within the same dosing group) experience a ≥Grade 3 AE of the same type that the Investigator considers reasonably attributable to VH4011499 and which leads to a decision to withdraw from the study (by Investigator or subject request).
- Two participants (within the same dosing group) have ≥Grade 2 intensity rash with systemic symptoms (e.g. fever, liver transaminase elevation and/or eosinophilia) that the Investigator considers reasonably attributable to VH4011499.
- Two participants (within the same dosing group) have a Grade 4 laboratory abnormality of the same type (regardless of causality assessment) or a Grade 3 laboratory abnormality of the same type which the Investigator considers reasonably attributable to VH4011499. Excluded from this are asymptomatic changes in lipid panel or creatine kinase changes with an alternative aetiology.

- Two participants (within the same dosing group) meeting liver stopping criteria (see Section 7.1.1)
- Two participants (within the same dosing group) with confirmed QTcF >500 msec or a change from baseline of QTcF >60 msec
- One sentinel participant (who received VH4011499) meeting any individual stopping criteria (see Section 7.1).
- Two participants (within the same dosing group) with clinically significant arrhythmias (Investigator judgment).

7.5. Site or Study Discontinuation

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations (Section 10).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Results that could unblind the study will not be reported to the investigative site or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of 56 days, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy and/or Immunogenicity Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

A brief/targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Single temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Body temperature measurements should be assessed according to site standard and should be measured at the same anatomical location throughout the study. Pulse oximetry will be assessed following each dose of midazolam (in Part 2, MAD/DDI dosing group(s) (See SoA, Section 1.3)).

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.

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). 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. 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 on the CRF.

8.2.3. Electrocardiograms

8.2.3.1. 12-lead Safety ECGs

12-lead ECG recordings will be obtained after the participant has been in a semi-supine position for at least 5 minutes using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Participant eligibility will be based upon triplicate ECG recordings. Single recordings will be made at all other time points.

Single 12-lead ECG 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. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

If the Investigator determines an ECG abnormality as clinically significant or is unable to determine the significance of abnormalities relating to rate, rhythm or intervals (including prolongation of the QT interval), then ECGs should be repeated in triplicate with recordings over a 5- minute time period. Refer to Section 7.1.2 QTc Stopping Criteria for QTc withdrawal criteria and additional QTc readings that may be necessary.

When triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

Safety ECGs may be printed from the Holter device. ECG parameters from safety ECGs will not be collected unless as part of an observed adverse event.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2: Clinical Laboratory Tests for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 21 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Sponsor medical monitor.

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.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

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).

8.2.5. Pregnancy Testing

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at weekly intervals during study intervention period.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1, Inclusion Criteria

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Pregnancy testing will be performed on all female participants at screening for eligibility but will not be required throughout the conduct of the study for female participants considered WONCBP since, to be eligible, they must be of non-childbearing potential.

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

The definitions of AEs or SAEs can be found in Section 10.3.
The definitions of unsolicited and solicited adverse events can be found in Section 10.3.

AEs will be reported by the participant.

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 all AEs that are serious, considered related to any study drug (including midazolam) or the study, or that caused the participant to discontinue the study (Section 7).

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

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

All SAEs will be collected from the signing of the ICF until the final follow-up visit specified in the SoA (Section 1.3).

All AEs will be collected from the start of intervention until the final follow-up visit.

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being

available.

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

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
  - Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

In Parts 1 and 3, female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

In Part 2, female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

Details of all pregnancies in female participants will be collected after the start of study drug and until 58 days after the last dose of study drug.

Details of all pregnancies in female partners of male participants will be collected after the start of study drug and until 118 days after the last dose taken by the male participant.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy. The site must obtain the necessary signed informed consent from the female partner. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The pregnant participant or pregnant partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

Any post-study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest are not evaluated in this study.

8.4. Pharmacokinetics

Blood Sample Collection

Whole blood PK and metabolite samples will be collected for measurement of plasma concentrations of VH4011499 (1 mL) and to assess for VH4011499-related material (2 mL for most timepoints, 5 mL for 12 h and 24 h post-dose) at the timepoints specified in the SoA (Section 1.3).

One whole blood sample of sufficient volume (typically 3 mL whole blood but will be

typically 5 mL or 6mL at 12 and 24 h post-dose timepoints, where applicable) will be processed into two aliquots of plasma: one to measure concentrations of VH4011499 and the other to characterize related metabolites. These samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

In Part 2, whole blood PK samples will also be collected for the measurement of plasma concentrations of midazolam and 1-hydroxymidazolam (2mL) at the timepoints specified in the SoA (Section 1.3).

Approximately 25-55 blood samples are planned to be collected to evaluate PK objectives for each part of the study. Additional samples may be collected during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Note: PK blood samples drawn after the last dose should be collected on an approximately 24-hour cycle (i.e., 24 hours post last dose, 48 hours post last dose, 72 hours post last dose, etc).

PK samples will be analysed using an appropriately validated assay method by or under the supervision of the sponsor.

The metabolite analyses will be conducted and reported separately from the main study report.

Urine Sample Collection

Urine metabolite samples will be collected at the time-points listed in the SoA (Section 1.3) and assayed for VH4011499-related material. Details of urine sample processing, storage and shipping procedures are provided in the SRM. The metabolite analyses will be conducted and reported separately from the main study report.

Entero-Tracker: Bile Sample Collection

Duodenal bile metabolite samples will be collected on Day 13 or Day 14 in Part 2 (MAD) dosing groups only. Collection of samples should be performed for each ascending MAD dosing group. Only the samples from the highest dosing group will be assayed for VH4011499- related material.

Bile fluid is recovered on a highly absorbent nylon line which is contained within a weighted gelatine capsule. The line unwinds after capsule swallowing as the capsule dissolves in the stomach and the line then passes into the duodenum. During withdrawal, the weighted section of the capsule separates from the line and passes in the stool.

Additional details of the bile Entero-Tracker sample collection, processing, storage and

shipping procedures are provided in the SRM. The metabolite analyses will be conducted and reported separate from the main study report.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

The OATP1B1/1B3 biomarker coproporphyrin I will be investigated in this study. Whole blood PK samples will also be collected for the measurement of plasma concentrations of coproporphyrin I (2mL) at the timepoints specified in the SoA (Section 1.3). Samples will be analyzed using an appropriately validated method under the supervision of the sponsor.

8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8. Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics 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 safety endpoints.

9.1. Statistical Hypotheses

The primary objectives of this study are to assess the safety and tolerability of VH4011499 in healthy participants following single (Parts 1 and 3) and multiple (Part 2) doses and describe the plasma pharmacokinetic characteristics of VH4011499 following single (Part 1) and multiple (Part 2) doses.

No formal statistical hypotheses are to be tested. Point estimates and corresponding confidence intervals will be constructed for any comparisons of interest (test:reference).

9.2. Analysis Sets

For purposes of analysis the following analysis sets are defined:

Analysis set	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who signed the ICF, passed screening and were randomized in the study.
Safety	All enrolled participants who take at least 1 full or partial dose of study treatment. Participants will be analysed according to the treatment they actually received.
VH499 PK	All participants in the Safety analysis set who have taken at least one full dose with at least one non-missing PK assessment. (Nonquantifiable values will be considered as non-missing values).

Further analysis sets may be defined in the SAP.

9.3. Statistical Analyses

9.3.1. General Considerations

In each part of the study data will be summarised by dosing group for VH4011499 and collectively from all dosing groups for placebo, unless otherwise specified.

For all endpoints, except for ECG, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Day 1 pre-dose ECGs for each dosing group will be performed in triplicate. In such case of triplicate measurement for pre-dose, the average will be used as baseline.

Continuous and categorical variables will be summarized using the following descriptive statistics, unless otherwise specified:

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

Confidence intervals for PK analyses will use 90% confidence levels, unless otherwise specified.

9.3.2. Primary Endpoint(s)/Estimands(s) Analysis

9.3.2.1. Safety Analyses

All primary safety analyses will be performed on the Safety analysis set.

Primary Endpoints	Statistical Analysis Methods
AEs	In each part, the number and proportion of participants reporting AEs will be tabulated by dosing group for VH4011499 and collectively for placebo. AEs will also be tabulated by severity and relationship to study drug. AEs will be tabulated using MedDRA preferred terms. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product. For part 2, AEs leading to study treatment withdrawal will also be summarized. In Part 1 and Part 3, discontinuation of study treatment can't occur as participants receive only 1 dose of study treatment. AEs will be summarized separately for each part of the study.

Primary Endpoints	Statistical Analysis Methods
Liver panel laboratory parameters	In each part, data for liver panel parameters will be summarised by dosing group for VH4011499 and collectively for placebo and by visit. Summary statistics (e.g. mean, median, std) for absolute values and for change from baseline will be presented. Summaries of maximum grade increase relative to Baseline will also be presented. Liver panel laboratory parameters will be summarised separately for each part of the study

Intercurrent Events

The intercurrent events mentioned in Section 3 along with the corresponding strategies will be considered during the analysis.

Study treatment discontinuation:

All available AE and liver panel data with respect to study treatment discontinuation will be used in AE summaries and summaries of liver panel data, respectively.

See Section 3 for a definition of primary safety estimands. More details on the primary safety analyses will be included in the SAP.

9.3.2.2. Pharmacokinetic Analyses

All primary pharmacokinetic analyses will be performed on the VH499 Pharmacokinetic analysis set.

Plasma VH4011499 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 8.1 or higher, Phoenix (Pharsight Corporation) or comparable software. Calculations for the final analysis, will be based on the actual sampling times recorded during the study. The various analyses will be conducted as data permits. Individual plasma PK parameters for each participant and dosing group will be determined, including but not limited to:

- Part 1 (single dose PiB): Cmax, tmax, t1/2 AUC(0-inf)
- Part 2 (repeated once daily [QD] dose) dosing groups without midazolam administration:
  - Day 1 (first Dose): Cmax, tmax
  - Day 14 (last Dose): AUC(0-t),Cmax, tmax, t1/2
- Part 2 (repeated once daily [QD] dose) dosing groups with midazolam administration:
  - Day 2 (first Dose): Cmax, tmax
  - Day 15 (last Dose): $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2}$

For a full list of the definition of pharmacokinetic parameters refer to Section 10.6.

Plasma VH4011499 concentrations will be presented in graphical and/or tabular form and will be summarized descriptively by dose. Plasma VH4011499 concentrations and PK parameters data will be summarized by dosing group and listed by participant within each part of the study. Descriptive summaries will be used as described in Section 9.3.1. More details will be provided in the SAP.

Intercurrent Events

The intercurrent events mentioned in Section 3 along with the corresponding strategies will be considered during the analysis.

Study treatment discontinuation:

Only serum concentration data available up to the time of study treatment discontinuation will be used in descriptive concentration data summaries and in derivation of PK parameters.

Any missing PK data due to study withdrawal will remain missing.

See Section 3 for a definition of primary PK estimands. More details on the primary PK analyses will be included in the SAP.

9.3.3. Safety Analyses

All safety analyses will be performed on the Safety analysis set. Within each part, summary statistics (e.g. mean, median, std etc.) of absolute values and change from Baseline values by visit and treatment arm (i.e. VH4011499 or placebo) will be presented for vital signs (e.g. blood pressure etc.), ECG (e.g. QTc, PR, QRS interval), coagulation (e.g. PT, PTT, INR), hematology and remaining chemistry laboratory parameters. Proportion of participants with maximum toxicity grade increase from Baseline will be presented by treatment arm for coagulation, hematology and remaining chemistry laboratory parameters. Details will be provided in the SAP.

CCI

CCI

9.3.5. Other Analysis

In Part 1 (and in Part 2, if data permits), dose proportionality will be assessed by the power model for PK parameters.

In Part 2, accumulation ratios will be evaluated by determining the ratio of last dose (i.e. Day 14 for dosing group 1 and optional dosing group 3 or 4, and Day 15 for dosing group 2 (and optional dosing group 3, if needed)) to first dose (i.e. Day 1 for dosing group 1 and optional dosing group 3 or 4, and Day 2 for dosing group 2 (and optional dosing group 3, if needed)) on C_{max}, $AUC_{(0-\tau)}$ and C_{τ} PK parameters.

In Part 2, attainment of steady-state will be assessed by estimating the slope of pre-dose trough concentrations using at least the last 3 pre-dose concentrations.

In Part 3, the log-transformed PK parameters (for VH4011499 tablet and for VH4011499 PiB from the same dose in Part 1) will be analyzed as data permits using a mixed effect model with a fixed effect term for tablet vs. PiB. Participant will be treated as a random effect in the model. Point estimates and 90% CIs for the ratios of tablet vs. PiB in PK parameters will be provided. Additional details will be provided in the SAP.

Special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the SAP.

9.3.6. Safety and PK dose escalation analyses

Refer to Section 10.1.5 for information on the dose escalation procedure. Further details about instream data review and the Safety and Dose Escalation Committee and process will be recorded in a Dose Escalation Plan document.

9.3.6.1. Bayesian dose escalation analyses

In the SAD part of the study, beginning with the second dose and for each subsequent dose, the Bayesian probability of any participant to exceed the CCI [redacted] at the subsequent dosing group will be calculated using PK data of participants who received VH4011499 in the previous dosing groups as appropriate. Observations on placebo are excluded. This probability, together with safety and tolerability data of the preceding dosing groups, will be used to help selection of the next dose. The Bayesian probability of exceeding the C_{max} NOAEL threshold can be calculated for additional potential doses to aid in dose selection, if necessary.

The Bayesian probability will be based on Whitehead's model shown below. [Whitehead, 2001] using non-informative prior for model parameters.

$$y_i = \theta_1 + \theta_2 d_i + \epsilon_i$$

Where y_i is log-PK of the i-th participant, d_i is the log-dose administered to the i-th participant. θ_1 and θ_2 are population intercept and slope, respectively, and ϵ_i is the random error of the i-th participant.

For the prediction of the second dose in Part 1 and Part 2, θ_2 will be assumed to equal 1 (representing a dose proportionality assumption). This will allow for the estimation of the remaining parameters of the model using data from only one dose level. After the second dose, θ_2 will be estimated by the data.

In the MAD part, the probability for either the maximum of C_{max} or maximum of AUC_{0-24} across all participants in the next dose to exceed the MAD PK stopping criteria (see section 7.4.1) will be calculated using similar Bayesian methodology.

9.3.6.2. Bayesian model Operating Characteristics (OC) – SAD part

In this part, we explore the operating characteristics of the Bayesian dose escalation model for a CCI [redacted], in an optional expansion dosing group (see Table 10 and Table 15). We are interested to calculate the probability to escalate the dose to a CCI [redacted] given that all previous possible doses (i.e. 25, 125, 600 and 1200 mg) have been administered successfully (see Table 15). This will occur when the posterior predictive probability that the C_{max} for any participant to exceed the CCI [redacted] is less than a threshold (i.e. 40%, 50%, 60%), given the data from

all previous doses. Additionally, we are interested in calculating the predicted maximum C_{max} among the 6 participants who will receive the CCI

Assuming $\theta_1 = \log(0.03)$ or $\log(1.82)$, $\theta_2 = 1$ (dose proportionality) and various between participant C_{max} variability values (geoCV = 30%, 40%, 50% and 60%) we simulated data for 10,000 virtual trials using Whitehead's model for each combination of θ_1, θ_2, and geoCV. $\log(C_{max})$ data were simulated from the distribution

$$\log(C_{max})_{ij} \sim N(\theta_1 + \theta_2 d_j, \sigma^2),$$

where $\theta_1 = \log(0.03)$ or $\log(1.82)$, $\theta_2 = 1$, d_j is the j-th log-dose administered to the i-th participant and σ^2 is the between participant variance of $\log(C_{max})$ calculated from the assumed geoCV.

The values of θ_1 are based on the predicted human C_{max} using preclinical data, based on two set of simulations that used different assumptions; one assumed a low bioavailability and the other high bioavailability. For each combination of θ_1, θ_2, and geoCV, each virtual trial contains simulated C_{max} values for 4 dosing groups (i.e. 25, 125, 600 and 1200 mg) of 6 participants each, for the prediction of the 2000 mg dose.

For each combination of θ_1, θ_2, and geoCV, for each simulated virtual trial, we fitted an MCMC procedure for $\log(C_{max})$ response using Whitehead's model with the following non-informative priors on the model parameters

$$\theta_1 \sim N(0, 1/0.01)$$

$$\theta_2 \sim N(1, 1/0.01)$$

$$1/\sigma^2 \sim \text{Gamma}(0.01, 0.01)$$

For each virtual trial, we calculated the Bayesian probability of an individual exceeding the C_{max} threshold in the following way:

We had 20,000 iterations in the MCMC procedure. In each iteration, we obtained the estimated parameters $\widehat{\theta_1}$, $\widehat{\theta_2}$, and $\widehat{\sigma^2}$ (the estimated variance of ϵ_i). Based on the estimation, a random sample of 20,000 values for each of the 6 participants was drawn from the distribution $N(\widehat{\theta_1} + \widehat{\theta_2} * \log(2000), \widehat{\sigma^2})$. This sample represents the predicted $\log(C_{max})$ for each participant with a possible highest dose of 2000 mg. The proportion of iterations with the simulated C_{max} for **any** participant exceeding the CCI is the Bayesian probability of any participant exceeding the CCI .

For each virtual trial, the Bayesian probability of any participant to exceed the NOAEL C_{max} with the highest dose is compared against different thresholds (i.e. 40%, 50% or 60%). Among the 10,000 simulated trials, the percentage of trials with Bayesian probability below the threshold (i.e. 40%, 50% or 60%) stands for the percentage of trials in which we would escalate CCI (Table 17), given that all previous possible doses (e.g., 25, 125, 600 and 1200 mg; see Table 15) have been administered.

Additionally, we calculated the predicted maximum C_{max} among the 6 participants planned to receive the CCI [redacted], by averaging the maximum C_{max} of the 6 participants across all MCMC iterations and virtual trials (Table 17).

Table 17 shows the predicted maximum C_{max} concentration among 6 participants planned to receive a CCI [redacted] (in an optional expansion dosing group) for various assumptions of θ_1 and geoCV, given that all previous possible doses have been administered successfully. It also shows the probability to escalate to CCI [redacted] using various thresholds (for decision making) for the probability of any participant to exceed the CCI [redacted] given that all previous doses have been administered successfully (e.g. in each simulated trial the estimated Bayesian probability of any participant to exceed the C_{max} NOAEL is compared against a threshold of 40% or 50% or 60%, and if it's higher then decision is not to CCI [redacted]). For example, assuming θ_1=log(1.82) and low between participant C_{max} variability (i.e. geoCV=30%) the probability to escalate to a CCI [redacted], given that all previous doses have been administered successfully, is 4% using a 40% threshold (conservative approach) for the probability of any participant to exceed the CCI [redacted] increases to 18% using a 60% (liberal approach) threshold.

Table 17 CCI [redacted]

θ1	**geoCV**	CCI [redacted]
log(0.03)	30%	
log(0.03)	40%	
log(0.03)	50%	
log(0.03)	60%	
log(1.82)	30%	
log(1.82)	40%	
log(1.82)	50%	
log(1.82)	60%	

Based on Table 16 assuming θ_1 = log(0.03) the predicted maximum C_{max} among the 6 participants on CCI [redacted] is much below the CCI [redacted] and all simulated trials had Bayesian probability of any CCI [redacted] below the thresholds of 40%, 50% and 60%, regardless of the assumed geoCV. So, if θ_1 =

log(0.03) as expected from simulations using preclinical data based on an assumption of low bioavailability, and all other assumptions hold (e.g. dose proportionality, i.e. $\theta_1 = 1$ etc.) it will be possible to escalate the[CCI], if needed, assuming all previous possible doses in SAD (e.g. 25, 125, 600 and 1200 mg; see Table 15) have been administered.

If $\theta_1 = \log(1.82)$, as expected from simulations using preclinical data based on an assumption of high bioavailability, and all other assumptions hold (e.g. dose proportionality, i.e. $\theta_1 = 1$ etc.) the probability to escalate [CCI], assuming all previous possible doses in SAD (e.g. 25, 125, 600 and 1200 mg; see Table 15) have been administered is low (i.e. <20%), regardless of the assumed between participant C_{max} variability (i.e. the assumed geoCV) and probability threshold.

9.3.6.3. Bayesian model Operating Characteristics (OC) – MAD part

In this section, we explore the operating characteristics of escalating to various top doses (for example, 500 mg, 500 mg) in the MAD part of the study given a starting dose of 200 mg.

Under different assumptions of between participant variability (%CVb = 20%, 40%) for Cmax and AUC0-24, PK data (in the log scale) were simulated for 10,000 virtual trials from a normal distribution with [CCI]. The means are based on predictions from a population PK model for the last dosing day in the first dosing group (for a dose of 200mg) in MAD, based on observed PK data from the first 3 dosing groups in the SAD part.

Each simulated trial contains Cmax and AUC0-24 values (in the log scale) for 6 subjects on treatment for a starting dose of 100 mg. Dose proportional jumps from 200 mg to either 500 mg or 700 mg were assumed. The same priors as in Section 9.3.6.2 were used in the Bayesian analysis for each PK parameter. No correlation between PK parameters was assumed. We assumed 8 participants in the top dose. We estimated (i) the proportion of virtual trials in which the Bayesian predictive probability (using simulated data from the starting dose of 200 mg) for at least one participant to have a Cmax or AUC0-24 above their respective NOAEL threshold (see Section 7.4.1) in the top dose is <50%, (ii) the predicted mean Cmax and AUC0-24 exposures across all participants in the top dose, and (iii) the predicted maximum Cmax and AUC0-24 across all participants in the top dose (see Table 18).

Table 18 Predicted mean and maximum Cmax and AUC0-24 across all participants in the top dose and probability of escalating to the reference top dose for various assumptions of data variability and top doses

Top Dose (mg)	Cmax Variability (%CVb)	AUC0-24 Variability (%CVb)	Predicted mean Cmax (95% CrI1) (ng/mL)	Predicted mean AUC0-24 (95% CrI) (ng/mL)	Predicted max Cmax (ng/mL)	Predicted max AUC0-24 (ng/mL)	Probability to escalate to top dose[2]
500	20%	20%	CCI [redacted]				
		40%					
	40%	20%					
		40%					
700	20%	20%					
		40%					
	40%	20%					
		40%					

[1]CrI = Credibility interval
[2]This was estimated as the proportion of virtual trials with Bayesian Predicted Probability <50%

These results indicate that there is a high probability of escalating close to a top dose of 500 mg, or even to 700 mg if data variability is not large, if the assumptions of the simulation hold.

9.4. Interim Analysis

There will be no formal interim analysis.

Preliminary safety, tolerability, and available PK data will be reviewed internally prior to each dose escalation and prior to initiation of Parts 2 and 3. Dose escalation can only occur after the SDEC has found that the safety and PK profiles are supportive to proceed with the evaluation of the next higher dose level (see Section 6.5).

Additional data cuts and analyses may be conducted to support regulatory needs, publications or for other purposes, if needed. Criteria for data quality for data released for these purposes will be described in the study data management plan.

9.5. Final Analyses

Final analyses will be performed after the completion of the study and final datasets authorization.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by participant, treatment and day; summaries will be presented by treatment, day, and time.

More details will be included in the SAP.

9.6. Sample Size Determination

Sample size for all parts of the study is based on feasibility and no formal calculation of power or sample size has been performed.

Parts 1 and 2

A sample size of approximately 6-8 active and 2 placebo participants per dosing group should be sufficient to provide useful estimates of both inter- and intra- participant variability for VH4011499 PK parameters and initial safety assessment.

Although the sample size is not based on statistical criteria, general probabilities can be determined for the likelihood of observing AEs. With 6 or 8 active participants per dosing group, if the true rate of an adverse event is 5%, the chance of seeing at least 1 participant with the adverse event for a given dosing group is 26% or 34%, respectively. Similarly, if the true adverse event rate is 20%, the chance of seeing at least 1 participant with the adverse event for a given dosing group is 74% or 83%, respectively.

For Part 2, for dosing groups in which midazolam is administered, with a sample size of 8 active participants, assuming a geometric CV_w for midazolam of 15% (estimated from

study 213052; GSK Document Number 2019N422949_01) for AUC(0-∞), the expected precision of the estimated ratio of midazolam AUC(0-∞) for midazolam + VH4011499 vs. midazolam will be as follows:

Drug	CV_w	Half-width (log-scale)	Ratio	90% CI
Midazolam	15%	0.141	0.9	(0.781, 1.037)
			1.0	(0.868, 1.152)
			1.1	(0.955, 1.267)

Part 3

To investigate the tablet PK a sample size of 6 active participants will be used in the dosing group using tablet formulation in Part 3.

The median of between-subject variability (geometric CVb) in VH4011499 PK parameters from the PiB administration across the first 3 dosing groups in SAD in this study were 26% and 30% for C_{max} and $AUC_{(0-\infty)}$, respectively.

Assuming a between-subject geometric coefficient of variation (CV_b) of 30% and a sample size of 6 active participants per group (i.e. PiB, tablet), it is estimated that the half width of the 90% CI for the formulation difference on the log-scale will be within 0.31 of the PK parameter (e.g. Cmax, $AUC_{(0-Inf)}$) point estimate. If the point estimate of the ratio of geometric means of PK parameters is assumed to be 1, then the 90% CI of the ratio will be approximately (0.74, 1.36).

9.6.1. Sample Size Sensitivity

Part 2 (dosing groups with midazolam administration)

A sensitivity analysis assuming a higher within-subject variability, CVw of 25% for midazolam $AUC_{(0-\infty)}$ and a sample size of 10 active participants was conducted. Table 19 below shows the expected precision of the estimated ratio of $AUC_{(0-\infty)}$ of midazolam for midazolam +VH4011499 vs. midazolam.

Table 19 Part 2 - MAD/DDI dosing group sample size sensitivity

Drug	N	CVw	Half-width (log-scale)	Ratio	90% CI
Midazolam	8	15%	0.141	0.9	(0.781, 1.037)
				1.0	(0.868, 1.152)
				1.1	(0.955, 1.267)
		25%	0.233	0.9	(0.713, 1.136)
				1.0	(0.792, 1.263)
				1.1	(0.871, 1.389)
	10	15%	0.122	0.9	(0.796, 1.017)
				1.0	(0.885, 1.130)
				1.1	(0.973, 1.243)
		25%	0.202	0.9	(0.735, 1.101)
				1.0	(0.817, 1.224)
				1.1	(0.899, 1.346)

The precision of the estimated ratio (i.e. 90% CI width) of midazolam $AUC_{(0-\infty)}$ midazolam +VH4011499 vs. midazolam increases only by ~14% when increasing the sample size from 8 to 10 participants in the VH4011499 arm.

Part 3

A sensitivity analysis assuming a higher between-subject variability, CV_b of 40% for PK parameters (e.g. Cmax, $AUC_{(0-\infty)}$) and a sample size of 10 active participants for the tablet formulation was conducted. Table 20 below shows the expected 90% CI of the ratio of geometric means for various assumed estimated ratios, as an example.

Table 20 Part 3 sample size sensitivity

NPiB	NTablet	CVb	Ratio	Estimated 90% CI
6	6	0.30	0.9	(0.662, 1.224)
			1	(0.736, 1.360)
			1.1	(0.809, 1.496)
		0.40	0.9	(0.601, 1.347)
			1	(0.668, 1.497)
			1.1	(0.735, 1.646)
	10	0.30	0.9	(0.689, 1.175)
			1	(0.766, 1.306)
			1.1	(0.842, 1.437)
		0.40	0.9	(0.634, 1.278)
			1	(0.704, 1.420)
			1.1	(0.775, 1.562)

The precision of the estimated ratio (i.e. 90% CI width) of PK parameters between VH4011499 tablet and VH4011499 PiB increases only by ~13% when increasing the sample size from 6 to 10 active participants in the VH4011499 tablet cohort.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:
Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines

Applicable ICH Good Clinical Practice (GCP) guidelines

Applicable laws and regulations

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:
Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC

Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

In case of unexpected pregnancy, participant must be informed that personal information such as date of birth and sex of the baby will be collected as part of safety follow-up. Consent for 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 personal information such as last menstrual period and year of birth, or the personal information of their baby such as date of birth and sex as part of safety follow-up.

If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

Participants who are rescreened are required to sign a new ICF.

VH/GSK (alone or working with others) may use participant’s coded study data and

samples and other information to carry out this study; understand the results of this study; learn more about VH4011499 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the the study drug approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding “No” box.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

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

10.1.5. Committees Structure (Safety and Dose Escalation Committee)

The study will utilize a SDEC which will include, at a minimum, the Sponsor medical monitor, clinical pharmacologist, and statistician to meet with the Investigator to make a dose escalation decision. Limited additional Sponsor representatives may be included on the SDEC. The SDEC will evaluate available data including but not limited to: AEs, vital signs, clinical laboratory findings, ECG parameters and PK data. In most cases the SDEC will meet when data are available for the entire dosing group through at least Day 7 assessments in Part 1 and at least Day 21 assessments in Part 2; however, there is allowance for the SDEC to meet when data are available for fewer participants in a dosing group (that is, at least 4 participants on active drug). The study will also utilize a SDEC for instream review of emerging PK and safety data in Part 3. In Part 3, the SDEC will plan to meet when data are available for the entire dosing group through at least Day 7 assessments. Limited data may be available for withdrawn participants. The blinding of personnel is discussed in Section 6.3. The construct and function of the SDEC will be documented in a charter.

10.1.6. Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a VH/GSK site or other mutually-agreeable location.

VH/GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.

Under the framework of the SHARE initiative, VH/GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

VH/GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis. The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with VH/GSK Policy.

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

10.1.7. 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 CRFs will be provided in eCRF completion guidelines.

Quality tolerance limits (QTLs) will be pre-defined in the QTL report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent CRO document.

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

VH/GSK or designee reserves the right to close the study site or terminate the study at any time for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- Discontinuation of further study intervention development For site termination:Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International

Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 21 will be performed by the local laboratory. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 21 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 count Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Percent reticulocytes White blood cell 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] Total protein Total and direct bilirubin Alkaline phosphatase[4] Aspartate aminotransferase (AST or SGOT)

Laboratory Assessments	**Parameters**
	Alanine aminotransferase (ALT or SGPT) Total Bile Acid (TBA)
Laboratory Assessments	**Parameters**
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)
Other Screening Tests	SARS-CoV-2 polymerase chain reaction test Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) 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], and hepatitis C virus antibody).

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5. 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 V H / 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 creatine phosphokinase 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 Chronic Kidney Disease Epidemiology Collaboration equation) at screening for eligibility determination.
4. 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.

Definition of Unsolicited and Solicited AE
• 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 participant 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.

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 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-

- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

An SAE is defined as any 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

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

- Every AE and SAE reported during the trial should be evaluated by the investigator and graded in the eCRF according to the DAIDS toxicity scales.
- **Note:** Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary.
- 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 following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to VH/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to VH/GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by VH/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide VH/GSK with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to VH/GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to VH/GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to VH/GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next SAE Reporting to VH/GSK via Paper Data Collection Tool) 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 off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next table on SAE Reporting to VH/GSK via Paper Data Collection Tool) or to the Sponsor medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to VH/GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor **medical monitor or the SAE coordinator**.

10.4. Appendix 4: Contraceptive and Barrier Guidance

As per Section 5.1 (Inclusion Criteria) of the protocol a female participant (female sex assigned at birth) is eligible to participate in this study if she is a woman of nonchildbearing potential (WONCBP) or a woman of childbearing potential (WOCBP) and is using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, during the study intervention period and for at least 58 days after the last dose of study intervention.

10.4.1. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. 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 or mIU/mLis 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. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (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 female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.3. Contraception Guidance

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

- **Agree to use a male condom** and should also be advised of the benefit for a female partner (if of child-bearing potential) to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

  AND

- **Female 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.

FOR FEMALE PARTNERS OF MALE PARTICPANTS CONSIDERED WOCBP, CONTRACEPTIVES[a] ALLOWED DURING THE STUDY 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 drug. 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)

Female participants considered WOCBP must agree to use contraception as detailed below:

- **Agree to use an additional highly effective contraceptive method** (with a failure rate of <1% per year), with low user dependency, during the study intervention period and for at least 58 days (e.g., 28- day post dose follow-up period plus 30 days (a menstrual cycle) after the last dose of study intervention. Highly effective, low user-dependency (with a failure rate of <1% per year) are limited to intrauterine devices/systems or bilateral tubal occlusion ≥3 months prior to screening.

Note: Documented evidence of contraception procedures (IUD/IUS/occlusion) below are required. Documentation can come from the site personnel's review of the participant's medical records.

FOR FEMALE PARTICIPANTS CONSIDERED WOCBP, CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly

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

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

Phase 1 Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology

Phase 1 Liver Chemistry Stopping Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND total bilirubin≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report as an SAE[1,2].</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study drug
• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column.
• Do not restart or rechallenge participant with study drug
• 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
• 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</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, one sample will be obtain as soon as possible in relation to the most recent dose. Another sample can be obtained as needed as dependent on the medical guidance[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• 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	medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study drug o In participants with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

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; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug 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 SRM.

10.6. Appendix 6: Abbreviations and Trademarks

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
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 = 0 hours to time = 24 hours
$AUC_{(0-tlast)}$	Area under the plasma concentration vs time curve from time = 0 hours to the time of last quantifiable concentration
$AUC_{(0-inf)}$	Area under the plasma concentration vs time curve from time = 0 hours to infinity
$AUC(0-\tau)$	Area under the plasma concentration vs time curve over a dosing interval from time of dosing to the time of the subsequent dose
BMI	Body mass index
CCI [redacted]	
C_{24}	Concentration at 24h Post-Dose
CAI	Capsid Inhibitor
CFR	Code of Federal Regulation
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent Oral Clearance
C_{max}	Maximum Observed Plasma Concentration
C_{last}	Concentration in a concentration time course
CPK	Creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
CPSR	Clinical pharmacology study report
CRF	Case Report Form
CSR	Clinical Study Report
C_{τ}	Concentration at the end of the dosing interval at steady state
CV	Coefficient of Variation
CVb	Between participant coefficient of variation
CVw	Within-subject variability
CYP	Cytochrome P450
DBL	Database lock
DDI	Drug-Drug Interaction
EC	Ethics committee
ECG	Electrocardiogram
EMEA	European Medicines Agency
ER	Extended Release
F	Bioavailability

FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First-time-in-human
FU	Follow-up
g	gram
g/L	Gram Per Litre
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
GSK	GlaxoSmithKline
h	Hour
Hb	Hemoglobin
HBV or HCV	Hepatitis B or C virus
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HED	Human Equivalent Dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICE	Intercurrent events
ICF	Informed Consent Form
ICH	International Council On Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalised Ratio
IRB	Institutional Review Boards
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVIVT	In Vitro/In Vivo Translation
Kg	Kilogram
m	Metre
LDH	Lactate Dehydrogenase
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MDZ	Midazolam
mg	Milligram
min	Minute
mL	Millilitre
mmHg	millimetre of Mercury

MRSD	Maximum Recommended Starting Dose
MSDS	Material Safety Data Sheet
ng	Nanogram
NOAEL	No observed adverse effect level
NQ	Nonquantifiable
PBPK	Physiologically based pharmacokinetic
PI	Principal Investigator
PiB	Powder-in-a-bottle
PK	Pharmacokinetic
PoC	Proof of Concept
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVR	Pulmonary Vascular Resistance
QD	Once-daily
QTc	Corrected QT Interval
QTcF	QT Interval Corrected for Heart Rate According to Fridericia's Formula
QTLs	Quality tolerance limits
RNA	Ribonucleic Acid
RHF	Right-Sided Heart Failure
RNA	Ribonucleic Acid
$R(AUC_{(0-\tau)})$	The accumulation ratio of AUC(0-inf): the ratio of AUC(0-inf) measured after the first dose and last dose in a multiple dose series
$R(C_{max})$	The accumulation ratio of C_{max}: the ratio of C_{max} measured after the first dose and last dose in a multiple dose series
$R(C_{\tau})$	The accumulation ratio of Cτ: the ratio of Cτ measured after the first dose and last dose in a multiple dose series
SAD	Single Ascending Dose
SAE	Serious adverse events
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SDEC	Safety and Dose Escalation Committee
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Apparent Terminal Elimination Phase Half-Life
t_{last}	Time of Last Quantifiable Plasma Concentration
t_{max}	Time to Cmax
TB	Tuberculosis
TQT	Thorough QT
TST	Tuberculin skin test
CCI [redacted]	
ULN	Upper Limit of Normal

US	United States
VSLC	ViiV Safety and Labelling Committee
V_z/F	Apparent Oral Volume of Distribution
WBC	White Blood Cells
WOCBP	Woman of childbearing potential
WONCBP	Woman of Non-Childbearing Potential

Trademark Information

Trademarks of the ViiV Healthcare and GSK group of companies
None

Trademarks not owned by the ViiV Healthcare and GSK of companies
EnteroTracker
WinNonlin

10.7. Appendix 7: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, July 2017

VERSION 2.1, July 2017

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

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

For more information, please refer to the DAIDS grading table Version 2.1, July 2017 at (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).

10.8. Appendix 8: 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 drug 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 drug 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.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, clinical investigators 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 drug, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

Clinical investigators should document in site files and the eCRF 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 must be withdrawn from study drug and discontinued from the study if he/she is found to have SARS-CoV-2 infection during an inpatient stay. The management of all other inpatient participants within the same dosing group should be discussed by the investigator and the medical monitor. Individuals who have not been exposed to the

virus will be permitted to remain in the clinic and fulfil their inpatient stay. Individuals who have been exposed will be discharged home regardless of whether they are symptomatic. Individuals who are discharged home may still be able to continue in the study at the discretion of the investigator and the medical monitor assuming the participant adheres to current Centers for Disease Control and Prevention guidance for exposure and assuming the participant continues to have a negative SARS-CoV-2 test status.

Participants who test positive during the outpatient phase of the trial 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.

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 Principal Investigator (PI) 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 PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI 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

1.9. Appendix 9: Protocol Amendment History

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

11. REFERENCES

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