Protocol Amendment 2

Study ID: 212548

Official Title of Study: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants

IND Number: 147773

EudraCT Number: 2020-002834-34

Date of document: 16-March-2021

TITLE PAGE

Protocol Title: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants

Protocol Number: 212548/ Amendment 02

Compound Number:	GSK3739937/VH3739937

Study Phase: Phase 1

Short Title: GSK3739937 First-Time-In-Human Study

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 1 919 438 2100

In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Research and Medical Strategy

This study is sponsored by ViiV Healthcare. Parexel with GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information: Refer to the Study Reference Manual

Regulatory Agency Identifying Number(s):

IND Number: 147773
EudraCT Number: 2020-002834-34

Approval Date: 16-MAR-2021

SPONSOR SIGNATORY

Protocol Title: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants

Protocol Number: 212548/ Amendment 02

Compound Number GSK3739937/VH3739937

Max Lataillade, DO, MPH Vice President, Head of Global Research Strategy ViiV Healthcare	**Date**

The signed page is a separate document.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment [02]	16-MAR-2021	TMF-11892450
Amendment [01]	11-JUN-2020	2019N400726_01
Original Protocol	20-APR-2020	2019N400726_00

Amendment [02]; 16-MAR-2021

Overall Rationale for the Amendment:

Updates made following acquisition of clinical pharmacology data in Part 1, the Single Ascending Dose (SAD) 10 mg, 30 mg, 80 mg, 160 mg, 320 mg and 640mg treatment periods and Multiple Ascending Dose (MAD) Cohort 3; 25 mg to:

- extend the period of post dosing assessment to include outpatient visits in the study;
- include a higher dose SAD treatment period (800 mg);
- revise the duration of dosing in MAD Cohort 5 (100 mg); and
- inclusion of an additional MAD Cohort 6 (500 mg) to evaluate weekly oral dosing.

Part 3 of the study was included to evaluate the relative bioavailability (RBA) of VH3739937 when administered as GSK3739937 powder-in-a-bottle (PiB) or as GSK3739937 100 mg Tablet under fasted and fed (moderate fat) conditions.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updates supporting conduct of additional 800 mg SAD treatment period, reduced dosing duration of MAD Cohort 5, weekly MAD Cohort 6 and Relative Bioavailability (RBA) and Food Effect (FE) cohort. Updated text regarding use of GSK3739937 (also known as VH3739937).	Revisions and updates based on observed longer PK half-life and observed safety data through to 640 mg SAD dose period and MAD Cohort 3. Sponsor decision to use GSK3739937 (also known as VH3739937) where indicated to further clarify Sponsor asset.
1.2 Schedule of Activities (SOA)	All SOA updated to include additional outpatient visits and assessments. SAD SOA revised to include additional treatment period. Update to support MAD Cohort 5 SOA reduced dosing duration. Addition of SOA for weekly MAD cohort and RBA and FE cohort	Revisions and updates to SOA were based on emerging PK data indicating longer PK half-life than anticipated and following review of emerging safety data and to support operational efficiencies
2.1 Study Rationale	Updates supporting conduct of additional 800 mg SAD treatment period, reduced dosing duration of MAD Cohort 5, weekly MAD cohort and Relative Bioavailability (RBA) and Food Effect (FE) cohort.	Revisions and update based on observed longer PK half-life and following review of emerging safety data
2.2.1 Background Key Safety and PK data with Prior Maturation Inhibitors (GSK3532795 and GSK3640254)	Inclusion of text to support conduct of additional 800 mg SAD treatment period, reduced dosing duration of MAD Cohort 5, and weekly MAD cohort.	To support updated study design based on emerging PK data indicating longer PK half-life than anticipated, a population model was conducted as an alternate analysis approach to characterize the pharmacokinetics and the simulation was implemented to predict higher single dose and multiple dose cohort PK profile based on the model

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Updates to risk assessment summarizing current safety data in study and to align with conduct of the updated study design. Clarification on gastric toxicity (effects on parietal cells and chief cells) and skin and subcutaneous tissue disorders (maculopapular rash)	To provide further clarification of risks based on current information
3.0 Objectives	Updates to objectives and endpoints in alignment with conduct of the updated study design.	Based on emerging PK data indicating longer half-life, updates were made to objectives and endpoints to support updated study design
4.1 Study Design	Updates supporting conduct of additional 800 mg SAD treatment period, reduced dosing duration of MAD Cohort 5, weekly MAD Cohort 6 and Relative Bioavailability (RBA) and Food Effect (FE) cohort.	Based on emerging PK data indicating longer half-life and following review of emerging safety data and to facilitate operational efficiencies
4.2 Scientific Rationale for Study design	Updates supporting conduct of additional 800 mg SAD treatment period, reduced dosing duration of MAD Cohort 5, weekly MAD Cohort 6 and Relative Bioavailability (RBA) and Food Effect (FE) cohort. Updates including summary of current safety data in study.	Revisions and updates were based on emerging PK data indicating longer PK half-life than anticipated and following review of emerging safety data and to support operational efficiencies
4.3.1 Predicted Human Pharmacokinetics	Updates summarizing predicted PK parameters are included.	To support updated study design based on emerging PK data indicating longer PK half-life than anticipated
4.3.2 Predicted Human Effective Dose	Updates summarizing predicted PK parameters	To support updated study design based on emerging PK data indicating longer PK half-life than

Section # and Name	Description of Change	Brief Rationale
	are included.	anticipated
4.3.3. Part 1 (SAD) Starting Dose and Dose Escalation	Revised text to align with the additional 800 mg dose SAD period based on emerging PK data	To support the updated study design based on emerging PK data indicating longer PK half-life than anticipated. Revision supported following review of emerging safety data.
4.3.4. Part 2 (MAD) Starting Dose and Dose Escalation	Revised text to align with the proposed daily MAD Cohort 5 and weekly MAD Cohort 6 based on emerging PK data	To support the updated study design based on emerging PK data indicating longer PK half-life than anticipated
4.3.5 Part 3 RBA Dose Selection	New section added	To support updated study design based on emerging PK data indicating longer PK half-life than anticipated and following review of emerging safety data and to facilitate operational efficiencies
4.3.6. Dose Escalation Committee	Revised text for dose escalation decision based on updated day of assessments in Part 1 and Part 2	Updated based on emerging PK data indicating longer PK half-life than anticipated
4.3.7. Anticipated Exposure and Safety Cover for a Range of Potential Doses	Updated table based upon predicted PK data outlining predicted safety and comparison to efficacy target and preclinical exposure.	To support the updated study design based on predicted PK data and based on observation of longer PK half-life than anticipated
5.1 Inclusion Criteria	Revised text to further clarify participants requirement for SARs-CoV-2 test frequency.	To mitigate risk to study conduct during the COVID-19 pandemic
5.3.1 Meals and Dietary Restrictions	Updated text with instructions on water intake, requirements and updated instructions on time period for dosing post food intake for relative bioavailability and food effect cohort, and	To facilitate conduct of the updated study design and outline requirements for Part 3 RBA and FE

Section # and Name	Description of Change	Brief Rationale
	updated day for bile test assessment.	
6. Study Intervention	Updated text regarding use of GSK3739937 (also known as VH3739937)	To further clarify the active investigation interventions used in study 212548 are GSK3733937 Powder in bottle (PiB) and GSK3733937 Tablet, 100 mg (can also be referred to as VH3733973 PiB and VH 3739937 Tablet, 100 mg)
6.1 Study Intervention(s) Administered	Revision to details of Study Interventions to include tablet for Part 3 of the study	Update with tablet study intervention
6.3 Method of Treatment Assignment	Revised text indicating RAMOS NG will not be used for SAD 800 mg period, weekly MAD cohort and RBA FE. Inclusion of randomization details for SAD 800 mg, weekly MAD Cohort 6 and RBA FE.	To support operational efficiencies of the updated study design
6.4 Measure to Minimize Bias: Randomization and Blinding	Updates describing randomization and blinding for Part 1 additional 800 mg SAD treatment period, and Part 2 weekly MAD cohort.	To further clarify randomization and blinding for the updated study design and to support operational efficiencies
6.6 Concomitant Therapy	Update to permitted medications	To permit vaccination with an approved vaccine for SARS-CoV-2 prior to or during study participation
7.1.4. PK Stopping Criteria for SAD and MAD	Updated text describing MAD PK stopping criteria for Part 2	Updated based on emerging PK data indicating longer PK half-life than anticipated
7.2 Participant Discontinuation /Withdrawal from the Study	Addition of text clarifying data to be collected at time of study discontinuation	To provide further clarification in study conduct

Section # and Name	Description of Change	Brief Rationale
8.1.3 Screening for COVID-19 Infection	Added text to clarify SARS-COV-2 testing upon admission to the unit, approximately one week prior to re-admission to unit, weekly while in the unit and at discharge.	To mitigate risk to study conduct during the COVID-19 pandemic
8.1.4. Electrocardiograms	Updated text to specify pre-dose and post-dose timepoint for 12-Lead ECG assessment in the study	To further assist in clarity for study conduct
8.4 Pharmacokinetics	Updated to include PK and metabolite sampling requirements for additional outpatient visits and assessments throughout the study in alignment with the updated SOA. Addition of text to expand use of Part 3 samples collected for VH3739937 plasma concentration.	Updated in alignment with the updated SOA. To support any additional analysis of samples collected for VH3739937 plasma concentration in Part 3
9.2.1 Sample Size Assumptions	New section added	Addition of text and 90% Confidence Intervals table to support Part 3 in the updated study design
9.2.2. Sample Size Sensitivity	Addition of text and table to support sample size sensitivity for Part 3.	To support Part 3 in the updated study design
9.4.3 Pharmacokinetic Analyses	Updated text to include individual plasma PK parameters for each participant and dosing group for Part 2 repeated once weekly dosing	To support updated study design based on emerging PK data indicating longer PK half-life than anticipated

Section # and Name	Description of Change	Brief Rationale
9.4.4 Statistical Analysis of Pharmacokinetic Data	Revised text to include accumulation evaluation for updated Cohort 5 and Cohort 6; Added text to describe assessment of RBA and FE.	To support updated study design and study objectives/endpoints
9.5 Interim Analyses	Updates to Bayesian model Operating Characteristic related to 800 mg SAD period, Part 2 MAD once daily dosing and weekly dosing	To support updated study design and study objectives/endpoints
10.1.8 Data Quality Assurance	Inclusion of text to clarify detailed information about study data collection and management process including systems used can be found in the study Data Management Plan	To further support sponsor or designee is responsible for data management of this study including quality checking of the data
10. 2 Appendix 2 Clinical Laboratory Tests	Addition of serum creatine phosphokinase to clinical laboratory tests	To further support routine clinical laboratory safety assessment
10.7 Appendix 7 Permissible Procedures during COVID-19 Pandemic	Added text to clarify requirement for SARS-COV-2 testing upon admission to the unit, approximately one week prior to re-admission to unit, weekly while in the unit and at discharge. Additional testing may be performed if deemed necessary.	To mitigate risk to study conduct during the COVID-19 pandemic
10.8 Appendix Abbreviations and Trademarks	Revised to include the abbreviations included in revisions in this protocol amendment	Inclusion of all abbreviations cited
10.9 Appendix 9 Protocol Amendment History	Updated with Overall Rationale for Protocol Amendment 1 and Summary of Changes table	For reference of overall rationale for protocol amendment 1 and summary of changes

Section # and Name	Description of Change	Brief Rationale
11. References	Updated with Investigator's Brochure Supplement Version 02	For reference of Investigator's Brochure Supplement Version 02

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants

Short Title: GSK3739937 First-Time-In-Human Study

Rationale: The inhibition of maturation and release of human immunodeficiency virus-1 (HIV-1) is a novel target for drug development, distinct from viral protease, reverse transcriptase and integrase. There are no maturation inhibitors (MI) approved for the treatment of HIV infection. GSK3739937 (also known as VH3739937) is a MI that displays *in vitro* evidence of low nanomolar potency against multiple HIV-1 Gag polymorphisms and a broad spectrum covering multiple HIV-1 subtypes, supporting compound development. This study is designed in three parts; i) to gain information on the safety, tolerability, and pharmacokinetic properties of VH3739937 when administered as powder-in-a-bottle (PiB); ii) the relative bioavailability (RBA) of the GSK3739937 PiB and GSK3739937 Tablet and; iii) to evaluate the safety, tolerability and pharmacokinetic (PK) parameters of the tablet formulation when administered under fasting and fed conditions. This study will enable further clinical development of VH3739937, including a Phase IIA Proof of Concept (PoC) study in HIV-infected patients and a First-Time-in-Human (FTiH) study of the long acting formulation of VH3739937.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To investigate the safety and tolerability of VH3739937 following single, repeated daily, and weekly oral administration in healthy participants (Part 1 & 2) • To assess the safety and tolerability of VH3739937 following single oral administration in healthy participants under fasted or fed (moderate calorie and fat) conditions (Part 3) • To evaluate the relative bioavailability (RBA) of GSK3739937 powder-in-bottle (PiB) versus GSK3739937Tablet and the effect of food on the PK of	VH3739937 safety parameters: • Adverse events (AEs); post baseline values and changes over time of clinical laboratory evaluations (haematology, clinical chemistry, urinalysis), vital signs, and electrocardiogram (ECG) parameters from pre-dose values (Parts 1, 2 and 3) Derived PK parameters for VH3739937: • Part 3 (single dose): $AUC_{(0-24)}$, $AUC_{(0-inf)}$, C_{max}

Objective	Endpoint
GSK3739937 Tablets and GSK3739937 PiB (Part 3)	
Secondary	
• To describe the pharmacokinetic (PK) profile of VH3739937 following single (Part 1 & 3), repeated daily and weekly (Part 2) oral administration in healthy participants	Derived PK parameters for VH3739937: • Part 1 (single dose): $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F • Part 2 (repeated once daily [QD] dose), as data permits: o Day 1: $AUC_{(0-24)}$, C_{max}, C_{24}, t_{max}, t_{lag} o Day 14 (Cohort 3 and 4): $AUC_{(0-t)}$, C_{max}, Ct, t_{max}, $t_{1/2}$, and CL/F o Day 18 (Cohort 5): $AUC_{(0-t)}$, C_{max}, Ct, t_{max}, $t_{1/2}$, and CL/F • Part 2 (repeated once weekly [QW] dose) o Day 1 (Cohort 6): $AUC_{(0-168)}$, C_{max}, C_{168}, t_{max}, t_{lag} o Day 15 (Cohort 6): $AUC_{(0-t)}$, C_{max}, Ct, t_{max}, $t_{1/2}$, and CL/F • Part 3 (single dose): C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F
• To examine dose proportionality following single and repeated doses of VH3739937 (Part 1 & 2)	Derived PK parameters for VH3739937: • Part 1 (single dose): $AUC_{(0-inf)}$, C_{max}. • Part 2 (repeated dose): $AUC_{(0-\tau)}$, C_{max}, $C\tau$
• To predict the accumulation from single dose data (Part 1) and assess accumulation of VH3739937 after repeat doses (Part 2 at steady state)	Accumulation indices for PK parameters for VH3739937: • Part 2 (repeated dose) Observed accumulation ratios: $RAUC_{(0-\tau)}$, $R(C_{max})$, $R(C\tau)$
• To assess time to steady-state of VH3739937 (Part 2)	Derived PK parameters for VH3739937: • Part 2 (repeated dose):

Objective	Endpoint
	○ Cohorts 3 and 4: Pre-dose concentrations on Day 2-14 ○ Cohort 5: Pre-dose concentrations on Day 2-18

$AUC_{(0-24)}$ = Area under the plasma concentration time curve from zero (pre-dose) to 24; $AUC_{(0-t)}$ = Area under the plasma concentration time curve from zero (pre-dose) to t; $AUC_{(0-inf)}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-τ) = Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state); C_{max} = Maximum observed concentration; t_{max} = Time of occurrence of C_{max}; $t_{1/2}$ = Apparent terminal phase half-life; t_{lag} = lag time; C_{24} = Drug concentration at 24 hours post-dose; C_{last} = last observable concentration; t_{last} = time of last observable concentration; C_{τ} (or C_{trough}) = trough serum concentration; CL/F= Apparent oral clearance; ECG= Electrocardiogram; PiB = powder-in-bottle; $RAUC_{(0-\tau)}$ = Accumulation ratio of area under the concentration-time curve over the dosing interval; $R(C_{max})$ = Ratio of maximum observed concentration; R (Cτ) = Ratio of concentration over the dosing interval; RBA = Relative Bioavailability

Overall Design and Schematic:

This study is a Phase 1, double-blind (sponsor-unblinded), randomized, placebo-controlled, single- and repeat-dose escalation study including a weekly oral dose (MAD) cohort and a relative bioavailability (RBA) and food effect (FE) cohort to investigate the safety, tolerability and PK of VH3739937 in healthy participants.

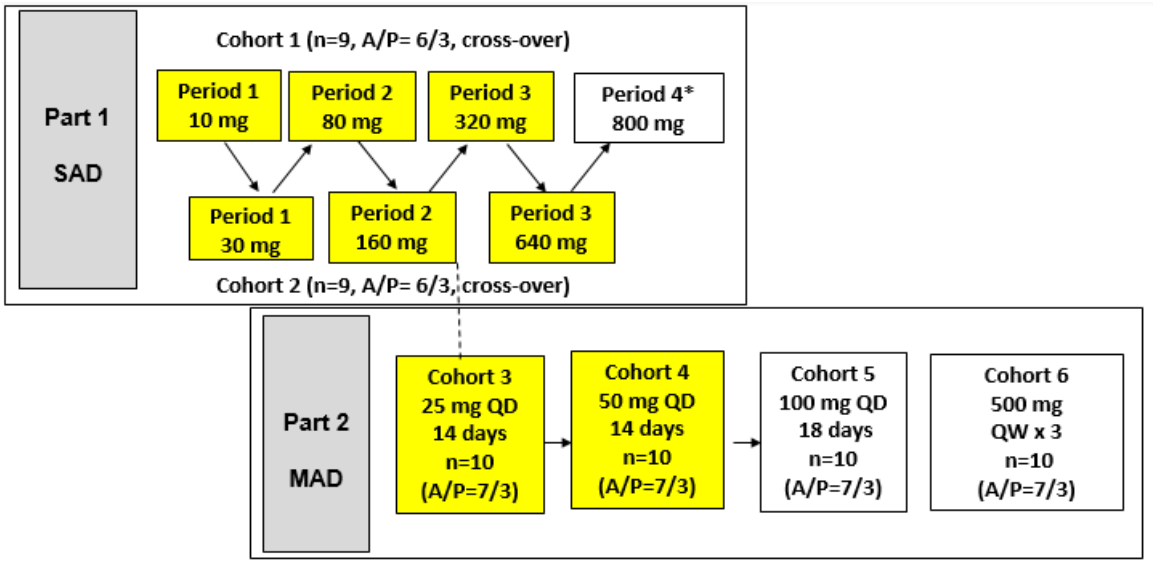
In Part 1, the proposed dosing schedule is designed to investigate single ascending dose (SAD) of oral VH3739937 initially in Cohorts 1 and 2. Then, at a suitable cross-over point (described below), Part 2 will involve 4 cohorts of multiple ascending dosing of oral VH3739937 when administered:

- once daily for 14 days (Cohorts 3 and 4);
- once daily for 18 days (Cohort 5); and
- three oral doses administered at weekly intervals over two weeks (Cohort 6) (Figure 1).

In Part 3, the RBA and FE (Cohort 7) will include a randomized, open-label, single dose, 3-period crossover design to compare the RBA of single doses of the GSK3739937 PiB with GSK3739937 Tablet, and to assess the effect of food (fasted or fed (under moderate calorie and fat conditions)) upon the safety, tolerability and PK of the GSK3739937 Tablet (Figure 2). All doses will be administered immediately following a standardized meal for each dosing period that contains approximately 600 calories with approximately 30% of calories from fat (unless otherwise indicated in Part 3 dosing in fasted condition).

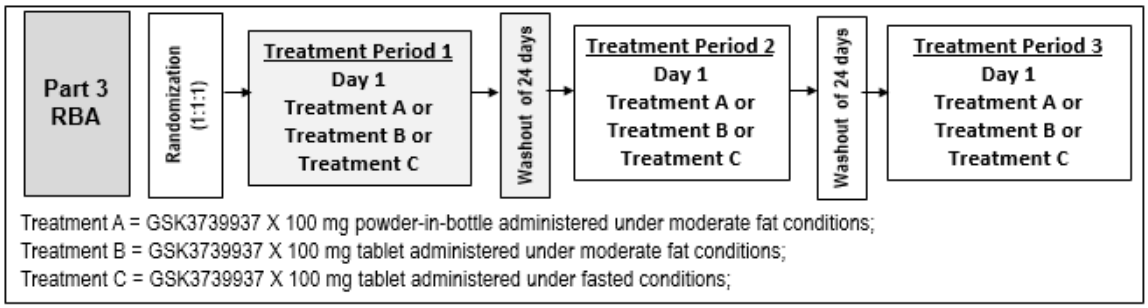
A summary of the overall study design, including doses, sample size, and order, is presented in Figure 1 and Figure 2 below.

Figure 1 Phase 1 Study in Healthy Participants using planned doses of VH3739937 Part 1 and Part 2



A=Active; P=Placebo
QD = once daily; QW = once weekly
*= Period 4 may include participants from both Cohorts 1 and 2
Highlighted cohorts and treatment periods denote completed

Figure 2 Phase 1 Study in Healthy Participants using planned doses of VH3739937 Part 3



Note: The doses shown in Figure 1 above are intended to demonstrate general concepts relating to factors of escalation. The modelling and simulation implemented using the data currently available following oral administration of a suspension formulation in the fed state indicated the predicted efficacious dose for the daily dose is 25 mg and the weekly dose is 500 mg. Due to the observed half-life of ~90 h, the anticipated accumulation ratio following repeated daily and weekly doses is ~ 6-fold and 1.3-fold, respectively. Dosing will be conducted in accordance with PK stopping criteria.

In Part 1, dose escalation will be determined by the Dose Escalation Committee (ViiV Healthcare (VH)/GlaxoSmithKline (GSK) study team and the Principal Investigator (PI))

and guided by safety data and PK stopping criteria. Post-dose safety and PK data through Day 16 from a minimum of 4 participants receiving VH3739937 are required for dose escalation in Part 1. The suitable crossover point from Part 1 to Part 2 referenced in the above text was determined once the single dose safety and preliminary PK data for the anticipated minimally effective dose was evaluated in Part 1 single ascending dose (SAD) and the maximum exposure for the MAD dose was covered by the SAD certain dose level. In Part 2, Cohorts 3 and 4, dose escalation will be determined by the VH/GSK study team and the PI and guided by the safety and PK data (minimally up to Day 29, 15 days following the Day 14 dose) from the previous dosing Cohort(s). Dose escalation from Cohort 5 will be similarly guided by safety and PK data minimally up to Day 33, 15 days following the Day 18 dose.

Based on human PK predicted from preclinical species, assuming an average bioavailability of ~14% and dose proportionality as well as predicted moderate between-participant PK variability, the highest dose to be assessed in Part 1 was anticipated to be ~640 mg QD. However, as indicated by data evaluated for Part 1 Treatment Periods through 640 mg, VH3739937 exposures are lower than predicted, therefore an additional higher dose SAD treatment period will be evaluated. This higher dose will be conducted in accordance with PK stopping criteria.

Disclosure Statement: This is a double-blind (sponsor unblinded) three-part study that includes two placebo-controlled single ascending dose cohorts (Part 1), four placebo-controlled multiple ascending dose cohorts (Part 2) and an open label RBA and FE cohort (Part 3).

Number of Participants:

Overall, approximately 76 participants will be randomly assigned to study intervention. In Part 1, approximately 18 participants will be randomized with approximately 9 participants within each of Cohort 1 and Cohort 2. Part 1 will include an additional higher dose treatment period (800 mg) evaluated in approximately 9 participants, as supported by emerging data. In Part 2, approximately 40 participants will be randomized with approximately 10 participants within each of Cohorts 3 to 6. In Part 3, approximately 18 participants will be treated to ensure that approximately 12 evaluable participants complete Cohort 7.

Participants will not be replaced if the reason for discontinuation from the study is due to a safety concern e.g. when a participant meets stopping criteria.

If participants prematurely discontinue the study for non-safety reasons in the SAD, they may be replaced at the discretion of the Sponsor in consultation with the investigator. The replacement participants will be assigned to the same treatment sequence, starting where the prior participant prematurely discontinued. Previously administered doses will not be repeated by replacement participants if dose escalation criteria are met.

If participants prematurely discontinue the study for non-safety reasons in the MAD, they may be replaced at the discretion of the Sponsor in consultation with the investigator. The replacement participants will be assigned to the same treatment in the same Cohort where the prior participant prematurely discontinued.

If participants prematurely discontinue Part 3, additional participants may be randomized after consultation with the sponsor to ensure that 12 evaluable participants complete the study.

Assignment of replacement numbers will be detailed in the Study Reference Manual (SRM).

Intervention Groups and Duration:

Part 1 (SAD):

The SAD portion of the study will be conducted in an interlocking fashion with two separate cohorts each of approximately 9 healthy participants. Each of these two cohorts may contain a minimum of 3 escalating doses of VH3739937 through to 640 mg. An additional 800 mg dose will be evaluated as this was indicated following review of safety and PK data from participants dosed up to 640mg. The interlocking design and the randomization sequence will allow the 9 participants in each cohort to potentially receive one of the lower and one of the higher doses of VH3739937. Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses). In each escalating dose period, 6 participants will be randomized to receive VH3739937 and 3 participants will be randomized to receive placebo (PBO). Each participant will receive PBO at least once. When the 800 mg dose is evaluated, 6 participants from both Cohorts 1 and 2 may be randomized to receive VH3739937 and 3 participants will be randomized to receive placebo, independent of which prior doses they received.

Dose escalation in Part 1 will be determined by the DEC (VH/GSK study team and the PI) based on the double-blind (sponsor-unblinded) safety data and the PK data from the current and previous dosing period(s) according to the dose escalation charter. Dose escalation will generally not exceed approximately 3-fold between doses up to approximately the predicted minimally effective dose and will not exceed 2-fold thereafter. However, if after the first SAD dose, the exposures are significantly different from the predicted level, the second dose or the sample collection schedule will be re-estimated and a different fold increase may be used. Post-dose safety and PK data through Day 16 from a minimum of 4 participants receiving VH3739937 are required for dose escalation in Part 1.

For Part 1 SAD, 24-hour continuous Holter/ ECG recordings will be collected on the day before dosing (Day -1), and Day 1 for extraction of ECGs paired with PK sampling.

Participants in Part 1 will have a screening visit within 28 days prior to the first dose and a follow-up visit approximately 28 days after the last dose. Flexibility of visit scheduling may be required if a pandemic situation applies (see Appendix 7). Otherwise, study assessments will be performed as indicated in the Schedule of Activities (SoA). Study participants will be confined to the clinic from Day −2 until discharge. Additional outpatient visits will be required on Days 9, 12 and 16. Duration of study participation in Part 1 may be a minimum of approximately 27 weeks for SAD treatment periods 1 to 3. However, in Part 1, study duration will be extended up to approximately 31 weeks to evaluate a higher dose (800 mg) for participants included in this dose period. Participants

who have completed Part 1 may be able to re-enroll to complete 800 mg treatment period. To ensure safety, participants will need to go through re-eligibility assessments.

Part 2 (MAD):

Part 2 (MAD) consists of approximately 4 ascending repeat-dose cohorts (Cohorts 3 to 6), each with 10 participants who will receive a once-daily dose of VH3739937 or PBO for 14 days (Cohorts 3 [25 mg] and 4 [50 mg]), or for 18 days (Cohort 5 [100 mg]), or three oral doses administered at weekly intervals over two weeks (Cohort 6 [500 mg]).

The duration of dosing in Cohort 5 is to support up to 18-day dosing as an oral lead for the future SAD and MAD studies of the long acting formulation of VH3739937. This duration is to potentially allow the identification of any early drug hypersensitivity reactions (HSR) which may occur before the administration of the long acting formulation. In each escalating dose cohort, 7 participants will be randomized to receive VH3739937 and 3 participants will be randomized to receive placebo (PBO). Dose escalation in Part 2 will be determined by the VH/GSK study team and the PI based on the double-blind (sponsor-unblinded) safety and PK data (minimally up to 15 days following the last dose) from the previous dosing Cohort(s). Specifically, safety and PK data through Day 29 in Cohorts 3 and 4, and through Day 33 in Cohort 5 from a minimum of 5 participants receiving active drug will be required for dose escalation.

Part 2 of the study was initiated once the single dose safety and preliminary PK data was evaluated in the SAD and the maximum exposure for the first MAD dose in Cohort 3 was covered by the SAD certain dose level. The potential minimally effective daily dose for VH3739937 with the suspension formulation was determined by the modeling and simulation utilising data for all doses in Part 1, as 25 mg, and is anticipated to be that which is predicted to provide a steady state $C\tau \geq 0.258$ μg/mL in 95% of participants.. More detailed information may be found in the IB Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025].

Dose escalation in the MAD will not exceed 2-fold between cohorts 3 to 5 and will be driven by safety and PK stopping criteria (see Section 7.1.4). The 500 mg dose included in the MAD Cohort 6 was determined following modelling and simulation of PK data acquired in the SAD treatment periods through to 640 mg and MAD Cohort 3. In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14 for Cohorts 3 and 4, on Day 18 for Cohort 5 and at Day 14 following the third QW dose in Cohort 6) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1).

For Part 2 MAD Cohorts 3, 4 and 5, 24-hour continuous Holter/ECG recordings will be collected, on the day before the first dose (Day -1), Day 1, and Day 14 for extraction of ECGs paired with PK sampling. In addition, 12-Lead ECGs will be collected for Part 2 at timepoints indicated in the SoA.

Participants in Part 2 will have a screening visit within 28 days prior to first dose and a follow-up visit approximately 28 days after the last dose. Flexibility of visit scheduling may be required if a pandemic situation applies (see Appendix 7). Otherwise, study assessments will be performed as indicated in SoA. Study participants will be confined to the clinic from Day −2 until discharge with requirement to complete all scheduled outpatient visits. Maximum duration of study participation from admission into the unit until completion of follow visit will be approximately 5 weeks.

Part 3 (RBA):

Part 3 is a randomized, open-label, single-dose, 3-period crossover optional Cohort 7 to compare the RBA of the GSK3739937 PiB with GSK3739937 Tablet and to assess the effect of food on the safety, tolerability and PK of GSK3739937 Tablet in healthy participants. In Part 3, approximately 18 participants will be treated to ensure that 12 evaluable participants complete Cohort 7. If participants prematurely discontinue Part 3, additional participants may be randomized after consultation with the sponsor to ensure that 12 evaluable participants complete the study.

Part 3 will consist of a screening period and 3 sequential treatment periods with a single dose of study intervention per treatment period.

Prior to dosing on Day 1 of Period 1, participants will be randomly assigned to 1 of 3 treatment sequences (ABC, BAC or CAB). Participants will receive each of the following treatments administered as 1 treatment per period:

- Treatment A: GSK3739937 PiB,100 mg (administered as oral suspension) administered under moderate fat conditions (reference)
- Treatment B: GSK3739937 Tablet, 100 mg (single dose given as a 100 mg tablet(s)) administered under moderate fat conditions (test)
- Treatment C: GSK3739937 Tablet, 100 mg (single dose given as 100 mg tablet(s))
  administered under fasted conditions (reference).

To ensure adequate washout, there will be at least 24 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 24 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

For treatments administered in the fed state, participants will fast overnight for at least 9.5 hours prior to dosing and will receive a moderate fat meal (Treatments A and B) 25 minutes prior to dosing. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing. Treatment C will be administered in the fasted state. For treatments administered in the fasted state, participants will fast overnight for at least 9.5 hours prior to dosing and until 4 hours after dosing.

Pharmacokinetic blood samples for the analysis of VH3739937 will be collected prior to dosing (0 hour) on Day 1 and up to 360 hours post-dose in Periods 1, 2 and 3. Additional outpatient visits up to approximately Day 16 post each Treatment A, B and C will be required for collecting necessary PK and safety assessments. Safety and tolerability will

be assessed by monitoring and recording of adverse events, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram results, and physical examination findings.

In Part 3, assessments will be performed as indicated in the SoA. Participants will be confined to the clinic from Day −2 until discharge on Day 6 of each treatment period. Participants are required to complete all outpatient visits during study conduct. Re-admission to the unit will occur on Day -2 for Treatment Periods 2 and 3. A washout period of 24 days is required during treatment periods 1 and 2 prior to dosing in subsequent treatment periods. The duration of Part 3, including Screening, is approximately 16 weeks.

Dose Escalation Committee: Yes (Part 1 and Part 2 only)

1.2. Schedule of Activities (SoA)

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the SoA, are essential and required for study conduct. This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA.

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

No more than 500 mL of blood will be collected over each 56-day period during the duration of the study, including any extra assessments that may be required.

When electrocardiogram (ECG) extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures will be carried out in said order.

PI will use initial screening data for all participants who are enrolled, randomized and dosed. All safety parameters will be reviewed by PI and VH/GSK study team members prior to the Dose Escalation Committee (DEC) making the decision to escalate dosing of participants at a higher dose.

Note:

- The Institutional Review Board/ Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF). The changes will be approved by the competent authorities and the ethics committee before implementation.
- The timing and number of planned study assessments, including safety, pharmacokinetic (PK), or other assessments 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.
- The duration and schedule of dosing in SAD and MAD cohorts and the doses to be administered may be altered during the course of the study, based on newly available data (e.g. to achieve Cmax and / or AUC levels required to optimize data acquisition including the generation of data closer to the time of peak plasma concentrations), to inform clinical development while ensuring study conduct in line with the PK and Safety Stopping Criteria.

- Any changes in the timing or addition of time points for any planned study assessments, or changes in the duration and schedule of dosing and the doses to be administered in the SAD and MAD cohorts, as the result of emerging PK 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.

Table 1 Screening and Follow-Up Assessments (Part 1, Part 2, and Part 3)[1]

Procedure	Screening (up to 28 days before Day 1)	Follow-Up[2] (approx. 28 days post last dose)	Notes
Outpatient Visit	X	X	
Informed Consent	X		
Inclusion/Exclusion Criteria and Demography	X		
Medical/medication/ drug/alcohol history	X		
Full Physical Examination	X	X	A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems
SARS CoV-2 Testing[2]	X		An approved molecular test (PCR) will be used. For further detail see Appendix 7 and Section 8.1.3
Columbia Suicide Severity Rating Scale (CSSRS)[2]	X		
Height, Weight, Body Mass Index (BMI)	X		
Vital signs	X	X	
12 Lead ECG	X	X	Triplicate ECGs will be used to determine participant eligibility at screening
Pregnancy Test	X	X	Follow up test may be obtained up to 37 days post last dose
Urine drug/alcohol/cotinine screen	X		Performed at the standard practice of the site
Hepatitis B surface antigen (HbsAg), Hepatitis C (HCV), Human immunodeficiency virus (HIV) tests[3]	X		If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required
Haematology/Chemistry/Urine tests	X	X	Laboratory procedures may be repeated and additional tests may be performed, if needed, at the discretion of the investigator.
Serious Adverse Event (SAE) Review	X	X	All SAEs will be collected from screening visit until the follow up visit
AE Review		X	All AEs will be collected from start of intervention until follow up visit
Concomitant Medication Review	X	X	

[1] In a pandemic situation see Appendix 7

[2]For early discontinuation that occurs prior to discharge from unit, SARS-CoV-2 testing, CSSRS, and final follow up assessments will be performed. For early discontinuation that occurs post discharge from unit, only final follow up assessments will be performed.

[3] HIV Ab/Ag 4th generation test (point of care test or laboratory immunoassay)

Table 2 Part 1 Single ascending dose (SAD) Study Intervention (Periods 1 through 4) – In Unit Duration

Procedure	Day -2	Day -1	Day 1 (Hours)														Day 2 (24 h)	Day 3 (48 h)	Day 4 (72 h)	Day 5 (96 h)	Day 6 (120 h)	Notes Hours (h) relate to PK sampling post last dose
			Pre-dose	0	1	2	3	4	5	6	7	8	9	10	12	16						
Admission to Unit	X																					In a pandemic situation see Appendix 7
Discharge from Unit																					X	In a pandemic situation see Appendix 7
Brief Physical Exam		X																X			X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the principal investigator (PI).
Weight, BMI		X																				
CSSRS																					X	
Vital signs		X	X		X	X		X	X	X					X		X	X	X	X	X	Vital signs to be performed pre-dose. Temperature will be monitored

Procedure	Day -2	Day -1	Day 1 (Hours)														Day 2 (24 h)	Day 3 (48 h)	Day 4 (72 h)	Day 5 (96 h)	Day 6 (120 h)	Notes Hours (h) relate to PK sampling post last dose
			Pre-dose	0	1	2	3	4	5	6	7	8	9	10	12	16						
																						every day during study participation. For further detail, see Section 8.1.2
12-lead safety ECGs		X	X		X	X		X		X					X	X	X	X	X	X	X	ECG timepoints may be reduced in subsequent dosing groups. For further detail, see Section 8.1.4.
Continuous ECG (full time matched baseline on Day-1)		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X					For further detail, see Section 8.1.4.
Pregnancy Test	X																				X	Female participants only. See Appendix 2
Testing for SARS CoV-2	X																				X	An approved molecular test (PCR) will be used. An additional SARS-CoV-2 test will be performed approximately

Procedure	Day -2	Day -1	Day 1 (Hours)														Day 2 (24 h)	Day 3 (48 h)	Day 4 (72 h)	Day 5 (96 h)	Day 6 (120 h)	**Notes** Hours (h) relate to PK sampling post last dose
			Pre-dose	0	1	2	3	4	5	6	7	8	9	10	12	16						
																						one week prior to re-admission to the unit. For further detail see Appendix 7and Section 8.1.3.
Drug/alcohol/cotinine screen	X																					
Haematology/Chemistry / Urine tests		X															X	X		X	X	For further detail, see Section Appendix 2
VH3739937 Dose Administration				X																		Randomization to occur on Day 1 prior to dosing. For meal instructions prior to dose, see Section 5.3.1
Meals	Per site usual practice																					
Plasma PK Sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	In Cohort 1, 4mL of blood will be collected for analysis at each timepoint. In Cohort 2, 2 mL of blood

Procedure	Day -2	Day -1	Day 1 (Hours)														Day 2 (24 h)	Day 3 (48 h)	Day 4 (72 h)	Day 5 (96 h)	Day 6 (120 h)	Notes Hours (h) relate to PK sampling post last dose
			Pre-dose	0	1	2	3	4	5	6	7	8	9	10	12	16						will be collected at each visit. For further detail, see Section 8.4.
Urine PK Sampling			X		<==========																	Pre-dose urine can be collected up to 3.5 h pre-dose. Afterward urine will be collected over 24 h collection periods as follows: 0-24 h, 24-48 h, 48 – 72 h, 72 – 96 h in Cohort 2 Period 3 only. For further detail, see Section 8.4.
SAE Review	<==========																					All SAEs will be collected from screening until follow up visit

Procedure	**Day -2**	**Day -1**	**Day 1 (Hours)**													**Day 2 (24 h)**	**Day 3 (48 h)**	**Day 4 (72 h)**	**Day 5 (96 h)**	**Day 6 (120 h)**	**Notes** Hours (h) relate to PK sampling post last dose
			Pre-dose	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**16**					
AE Review			<==========																	==========>	All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========																			==========>	

Table 2 continued Part 1 SAD Cohorts 1 and 2 Periods 1 through 4 – Outpatient Visit

Procedure	Day			Notes Hours (h) relate to PK sampling post last dose
	9 (192 h)	12 (264 h)	16 (360 h)	
Outpatient Visit	X	X	X	
Brief Physical Exam	X	X	X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
Vital signs	X	X	X	For further detail, see Section 8.1.2
12-lead safety ECGs	X	X	X	For further detail, see Section 8.1.4
Haematology/Chemistry/ Urine tests	X	X	X	For further detail, see Section Appendix 2
Plasma PK Sampling	X	X	X	In Cohort 1, 4mL of blood will be collected for analysis at each timepoint. In Cohort 2, 2 mL of blood will be collected at each visit. For further detail, see Section 8.4.
Urine PK Sampling	X	X	X	For Cohort 2 Period 3 only, fresh spot urine sample collection at each visit. Please see SRM for further detail.
SAE/AE Review	<==========		==========>	All SAEs will be collected from screening until follow up visit; All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========		==========>	

Table 3 Part 2 Multiple ascending dose (MAD) Cohorts 3 and 4: Study Intervention - In Unit Duration

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	-1	1	2, 4, 6, 8, 10, 12, 14	3, 5, 7, 9, 11, 13	15 (24 h)	16 (48 h)	17 (72 h)	18 (96 h)	19 (120 h)	Hours (h) relate to PK sampling post last dose
Admission to Unit	X										In a pandemic situation see Appendix 7.
Discharge from Unit										X	In a pandemic situation see Appendix 7
Brief Physical Exam		X		X (Day 6)		X				X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
CSSRs				X (Day 12)						X	
Weight, BMI		X								X	
Vital signs		X	X	X			X		X	X	Vital signs to be performed pre-dose. Temperature will be monitored every day during study participation. For further detail, see Section 8.1.2
12-lead safety ECGs		X	X	X	X (Day 3)	X	X	X	X	X	ECG should be performed pre-dose on dosing days. ECG timepoints may be reduced in subsequent dosing groups. For further detail, see Section 8.1.4
Continuous ECG (full time matched baseline on Day-1)		X	X	X (Day 2 end of 24 h collection from Day 1 and Day 14)		X (end of 24 h collection from Day 14)					Continuous ECG monitoring from Day -1 to 24 h post dose on Day 1 and 14. ECG data extraction will coincide with PK sampling schedule at pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 h post dose on Days 1,

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	-1	1	2, 4, 6, 8, 10, 12, 14	3, 5, 7, 9, 11, 13	15 (24 h)	16 (48 h)	17 (72 h)	18 (96 h)	19 (120 h)	Hours (h) relate to PK sampling post last dose
											2, 14 and 15 and on corresponding timepoints on Day -1. For further detail, see Section 8.1.4
Testing for SARS CoV-2	X			X (Day 14)	X (Day 7)					X	An additional SARS-CoV-2 test will be performed approximately one week prior to admission to the unit. Weekly SARS-CoV-2 testing is required while in the unit (Days 7 and 14) and on discharge (Day 19). An approved molecular test (PCR) will be used. For further detail, see Appendix 7 and Section 8.1.3.
Drug/alcohol/cotinine screen	X										
Haematology/Chemistry / Urine tests		X	X	X			X		X	X	For further detail, see Appendix 2
Pregnancy Test	X										Female participants only. For further detail see Appendix 2
VH3739937 Dose Administration			X	X	X						Once-daily oral dose from Day 1 to Day 14. Randomization to occur on Day 1 prior to dosing. For meal instructions prior to dose, see Section 5.3.1
Meals	Per site usual practice										
Plasma PK Sampling			X	X	X (Day 3, 11 and 13)	X	X	X	X	X	2mL of blood will be collected at pre-dose (within 15 mins prior to dosing) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24h post

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	-1	1	2, 4, 6, 8, 10, 12, 14	3, 5, 7, 9, 11, 13	15 (24 h)	16 (48 h)	17 (72 h)	18 (96 h)	19 (120 h)	Hours (h) relate to PK sampling post last dose
											dosing on Day 1 and Day 14. The 24 hour post Day 1 dose collection will be pre-dose on Day 2, the 24 hour post Day 14 dose collection will be post dose on Day 15 (24 hours after the last dose). Samples will also be collected pre-dose on Days, 3, 4, 6, 8, 10, 11,12, 13 and once each day on days 16 (48 hours post last dose),17(72 hours post last dose),18 (96 hours post last dose) and 19 (120 hours post last dose). PK sampling timepoints may be reduced. For further detail, see Section 8.4
Plasma Metabolite Sampling			X	X (Day 2 and Day 14)		X					Additional 2mL of blood will be collected at pre-dose (within 15 mins prior to dosing) and at the same timepoints as Plasma PK samples on Days 1, 2, 14 and 15 (as described above). For further detail, see Section 8.4
Urine PK and Metabolite Sampling			X	X (Day 2 end of 24 h collection from Day 1 and on Day 14)		X (end of 24 h collection from Day 14)	X	X	X	X	Collections at pre-dose (20 mL) (within 1 h prior to dosing) and from time 0 up to 24 h post dosing on Day 1 and from time 0 to 24h post dosing on Day 14. Spot urine sample collection on Day 16, 17, 18, and 19 at the post dose timepoint utilized on

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	**-1**	**1**	**2, 4, 6, 8, 10, 12, 14**	**3, 5, 7, 9, 11, 13**	**15 (24 h)**	**16 (48 h)**	**17 (72 h)**	**18 (96 h)**	**19 (120 h)**	Hours (h) relate to PK sampling post last dose
											Day 1. For further detail, see Section 8.4
SAE Review	<==========									==========>	All SAEs will be collected from screening until follow up visit
AE Review			<==========							==========>	All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========									==========>	

Table 3 continued Part 2 MAD Cohorts 3 and 4 – Outpatient Visit

Procedure	Day			Notes Hours (h) relate to PK sampling post last dose
	22 (192 h)	**25 (264 h)**	**29 (360 h)**	
Outpatient Visit	X	X	X	
Brief Physical Exam	X	X	X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
Vital signs	X	X	X	For further detail, see Section 8.1.2
12-lead safety ECGs	X	X	X	For further detail, see Section 8.1.4
Haematology/Chemistry/ Urine tests	X	X	X	For further detail, see Appendix 2
Plasma PK Sampling	X	X	X	About 2 mL of blood will be collected at each visit.
Urine PK Sampling	X	X	X	Fresh spot urine sample collection at each visit. Please see SRM for further detail.
SAE/AE Review	<==========		==========>	All SAEs will be collected from screening until follow up visit; All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========		==========>	

Table 4 Part 2 MAD Cohort 5: Study Intervention (Day-2 to Day 23) – In Unit Duration

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	-1	1	2, 4, 6, 8, 10, 12, 14, 16, 18	3, 5, 7, 9, 11, 13, 15, 17	19 (24 h)	20 (48 h)	21 (72 h)	22 (96 h)	23 (120 h)	Hours (h) relate to PK sampling post last dose
Admission to Unit	X										In a pandemic situation see Appendix 7.
Discharge from Unit										X	In a pandemic situation see Appendix 7
Brief Physical Exam		X		X (Day 18)	X (Day 9)					X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
CSSRs				X (Day 18)	X (Day 9)					X	
Weight, BMI		X								X	
Vital signs		X	X	X	X (Days 15 and 17)		X		X	X	Vital signs to be performed pre-dose. Temperature will be monitored every day during study participation. For further detail, see Section 8.1.2
12-lead safety ECGs		X	X	X	X (Days 3, 15 and 17)	X	X	X	X	X	ECG should be performed pre-dose on dosing days. ECG timepoints may be reduced in subsequent dosing groups. For further detail, see Section 8.1.4
Continuous ECG (full time matched baseline on Day-1)		X	X	X (Day 2 - end of 24 h collection from Day 1 and Day 14)	X (Day 15 - end of 24 h collection from Day 14)						Continuous ECG monitoring from Day -1 to 24 h post dose on Day 1 and 14. ECG data extraction will coincide with PK sampling schedule at pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 h post dose on Days 1, 2, 14 and

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	-1	1	2, 4, 6, 8, 10, 12, 14, 16, 18	3, 5, 7, 9, 11, 13, 15, 17	19 (24 h)	20 (48 h)	21 (72 h)	22 (96 h)	23 (120 h)	Hours (h) relate to PK sampling post last dose
											15 and on corresponding timepoints on Day -1. For further detail, see Section 8.1.4
Testing for SARS CoV-2	X			X (Day 14)	X (Day 7)					X	An additional SARS-CoV-2 test will be performed approximately one week prior to admission to the unit. Weekly SARS-CoV-2 testing is required while in the unit (Days 7, 14) and on discharge (Day 23). An approved molecular test (PCR) will be used. For further detail see Appendix 7 and Section 8.1.3
Drug/alcohol/cotinine screen	X										
Haematology/Chemistry/ Urine tests		X	X	X	X (Day 15)		X		X	X	For further detail, see Appendix 2
Pregnancy Test	X									X	Female participants only. For further detail see Appendix 2
VH3739937 Dose Administration			X	X	X						Once-daily oral dose from Day 1 to Day 18. Randomization to occur on Day 1 prior to dosing. For meal instructions prior to dose, see Section 5.3.1
Meals	Per site usual practice										
Plasma PK Sampling			X	X	X (Days 3, 15, 17)	X	X	X	X	X	2mL of blood will be collected pre-dose (within 15 mins prior to dosing) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24h post dosing on Days 1, 14 and Day 18. The

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	-1	1	2, 4, 6, 8, 10, 12, 14, 16, 18	3, 5, 7, 9, 11, 13, 15, 17	19 (24 h)	20 (48 h)	21 (72 h)	22 (96 h)	23 (120 h)	Hours (h) relate to PK sampling post last dose
											24 hour post Day 1 dose collection will be pre-dose on Day 2, the 24 hour post Day 14 dose collection will be post-dose on Day 15 and the 24 hour post Day 18 dose will be post dose on Day 19 (24 hours after the last dose). At all other timepoints on dosing days, samples will be drawn pre-dose prior to dose administration. On post dosing Days 20, 21, 22 and 23 samples will be collected at the same time of the day as the post-dose collections on dosing days. PK sampling timepoints may be reduced. For further detail, see Section 8.4
Plasma Metabolite Sampling			X	X (Days 2, 14 and 18)	X (Day 15)	X					Additional 2mL of blood will be collected pre-dose (within 15 mins prior to dosing) and at the same timepoints as Plasma PK samples on Days 1, 2, 14, 15, 18 and 19 (as described above). For further detail, see Section 8.4
Urine PK and Metabolite Sampling			X	X (Day 2 end of 24 h collection from Days 1, 14 and Day 18)	X (Day 15 end of 24 h collection from Day 14)	X (Day 19 end of 24 h collection	X	X	X	X	Collections at pre-dose (40 mL) (within 1 h prior to dosing) and from time 0 up to 24 h post dosing on Days 1, 14 and 18. Spot urine sample collection on

Procedure	Pre-Treatment Days		Treatment Days			In House Post Treatment Days					Notes
	-2	**-1**	**1**	**2, 4, 6, 8, 10, 12, 14, 16, 18**	**3, 5, 7, 9, 11, 13, 15, 17**	**19 (24 h)**	**20 (48 h)**	**21 (72 h)**	**22 (96 h)**	**23 (120 h)**	Hours (h) relate to PK sampling post last dose
						from Day 18)					Day 20, 21, 22, and 23. For further detail, see Section 8.4
Bile Sampling (Enterotest or EnteroTracker)				X (Day 18)							Collection at pre-dose and post dose via Enterotest or Enterotracker. Enterotest or Enterotracker will be swallowed at 2 h post dose. After approx. 6.5 h the string will be removed. For Further detail see Section 5.3.1
SAE Review	<==========									==========>	All SAEs will be collected from screening until follow up visit
AE Review			<==========							==========>	All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========									==========>	

Table 4 continued: Part 2 MAD Cohort 5: Outpatient Visits

Procedure	Day			Notes Hours (h) relate to PK sampling post last dose
	26 (192 h)	**29 (264 h)**	**33 (360 h)**	
Outpatient Visit	X	X	X	
Brief Physical Exam	X	X	X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
Vital signs	X	X	X	For further detail, see Section 8.1.2
12-lead safety ECGs	X	X	X	For further detail, see Section 8.1.4
Haematology/Chemistry/ Urine tests	X	X	X	For further detail, see Appendix 2
Plasma PK Sampling	X	X	X	About 2 mL of blood will be collected at each visit.
Urine PK Sampling	X	X	X	Fresh spot urine sample collection at each visit. Please see SRM for further detail.
SAE/AE Review	<==========		==========>	All SAEs will be collected from screening until follow up visit; All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========		==========>	

Table 5 Part 2 Weekly MAD Cohort 6: Study Intervention – In Unit Duration

Procedure	Pre-Treatment Days		Week 1 Treatment Days		Week 2 Treatment Days		Week 3 Treatment Days	In House Post Treatment Days					Notes
	-2	-1	1	2, 3, 4, 5, 6, 7	8	9, 10, 11, 12, 13, 14	15	16 24h	17 48h	18 72h	19 96h	20 120h	Hours (h) relate to PK sampling post last dose
Admission to Unit	X												In a pandemic situation see Appendix 7.
Discharge from Unit												X	In a pandemic situation see Appendix 7
Brief Physical Exam		X		X (Day 6)		X (Day 9)	X					X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
CSSRs						X (Day 12)						X	
Weight, BMI		X										X	
Vital signs		X	X	X (Days 2, 4, and 6)	X	X (Days 10, 12 and 14)	X	X		X		X	Vital signs to be performed pre-dose. Temperature will be monitored every day during study participation. For further detail, see Section 8.1.2
12-lead safety ECGs		X	X	X	X	X	X	X	X	X	X	X	ECG should be performed pre-dose on dosing days. ECG timepoints may be reduced in subsequent dosing groups. For further detail, see Section 8.1.4
Testing for SARS CoV-2	X			X (Day 7)		X (Day 14)						X	An additional SARS-CoV-2 test will be performed approximately one week prior to admission to the unit. Weekly SARS-CoV-2 testing is required while in the unit (Days 7, 14) and on discharge (Day 20). An approved molecular

Procedure	Pre-Treatment Days		Week 1 Treatment Days		Week 2 Treatment Days		Week 3 Treatment Days	In House Post Treatment Days					Notes
	-2	-1	1	2, 3, 4, 5, 6, 7	8	9, 10, 11, 12, 13, 14	15	16 24h	17 48h	18 72h	19 96h	20 120h	Hours (h) relate to PK sampling post last dose
													test (PCR) will be used. For further detail see Appendix 7 and Section 8.1.3
Drug/alcohol/nicotine screen	X												
Haematology/Chemistry/ Urine tests		X	X	X (Days 2, 4 and 6)	X	X (Days 9, 11 and 13)	X		X		X	X	For further detail, see Appendix 2
Pregnancy Test	X												Female participants only. For further detail see Appendix 2
VH3739937 Dose Administration			X		X		X						Weekly oral dose on Days 1, 8 and 15. Randomization to occur on Day 1 prior to dosing. For meal instructions prior to dose, see Section 5.3.1
Meals	Per site usual practice												
Plasma PK Sampling			X	X	X	X	X	X	X	X	X	X	2mL of blood will be collected at pre-dose (within 15 mins prior to dosing) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 16 h on Days 1, 8 and Day 15. The 24 h post day 1 dose collection on Days 2, 9 and 15 will be taken at post-dose collection timepoint. At all other timepoints on non-dosing days (Days 3, 4, 5, 6, 7, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20), samples will be drawn at the post-dose

Procedure	Pre-Treatment Days		Week 1 Treatment Days		Week 2 Treatment Days		Week 3 Treatment Days	In House Post Treatment Days					Notes
	-2	-1	1	2, 3, 4, 5, 6, 7	8	9, 10, 11, 12, 13, 14	15	16 24h	17 48h	18 72h	19 96h	20 120h	Hours (h) relate to PK sampling post last dose
													timepoint. For further detail, see Section 8.4
Urine PK			X	X (Day 2, end of 24hr collection from Day 1)	X	X (Day 9, end of 24hr collection from Day 8)	X	X (Day 16, end of 24hr collection from Day 15)					Collections at pre-dose (20 mL) (within 1 h prior to dosing) and from time 0 up to 24 h post dosing on Days 1, 8 and 15. For further detail, see Section 8.4
SAE Review	<==========											==========>	All SAEs will be collected from screening until follow up visit
AE Review			<==========									==========>	All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========											==========>	

Table 5 continued: Part 2 Weekly MAD Cohort 6: Outpatient Visit

Procedure	Day			Notes Hours (h) relate to PK sampling post last dose
	23 (192 h)	26 (264 h)	30 (360 h)	
Outpatient Visit	X	X	X	
Brief Physical Exam	X	X	X	Brief physical examinations may be made full and laboratory procedures may be repeated if needed at the discretion of the PI.
Vital signs	X	X	X	For further detail, see Section 8.1.2
12-lead safety ECGs	X	X	X	For further detail, see Section 8.1.4
Haematology/Chemistry/ Urine tests	X	X	X	For further detail, see Appendix 2
Plasma PK Sampling	X	X	X	About 2 mL of blood will be collected at each visit.
Urine PK Sampling	X	X	X	Fresh spot urine sample collection at each visit. Please see SRM for further detail.
SAE/AE Review	<==========		==========>	All SAEs will be collected from screening until follow up visit; All AEs will be collected from first dose until follow up visit
Concomitant Medication Review	<==========		==========>	

Table 6 Part 3 RBA Cohort 7: Study Intervention – In Unit Duration and Outpatient Visits

Procedure	Pre-Treatment Days		Treatment Periods 1 and 2 (Days)								Treatment Period 3 only (Days)							Notes
				Washout								Washout						Hours (h) relate to PK sampling post last dose
	-2	-1	1	2	3 -5	6	9	12	16	17-22	1	2	3-5	6	9	12	16	
Admission to Unit	X																	For all treatment periods, 24 day required wash out includes completion of re-admission to unit on Day -2 and Day -1 for subsequent treatment periods. Admission to unit will occur on Day-2 for all treatment periods.
Discharge from clinic						X								X				Discharge from unit at discretion of PI during pandemic
Outpatient Visit							X	X	X						X	X	X	
Brief Physical Exam		X				X	X	X	X					X	X	X	X	Brief physical examinations may be made full examinations if needed, at the discretion of the investigator
Pregnancy Test	X																	Female participants only. For further detail see Appendix 2

Procedure	Pre-Treatment Days		Treatment Periods 1 and 2 (Days)								Treatment Period 3 only (Days)							Notes
				Washout								Washout						Hours (h) relate to PK sampling post last dose
	-2	-1	1	2	3 -5	6	9	12	16	17-22	1	2	3-5	6	9	12	16	
SARS-CoV-2 Test	X					X								X				An approved molecular test (PCR) will be used. If participants remain in unit during study treatment periods, weekly SARS-CoV-2 testing is required. If participants are discharged from unit on Day 6, SARS-CoV2 test will be required at discharge, approximately one week prior to re-admission to the unit for the following period and at Day -2. For further detail, see Appendix 7 and Section 8.1.3
Drug/alcohol/ nicotine screen	X																	
Vital Signs		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	Blood pressure and pulse will be measured in triplicate pre-dose on Day 1 in Periods 1-3. At all other timepoints, single blood pressure and pulse will be measured at pre-dose timepoint. Temperature will be monitored every day during study participation. For further detail, see Section 8.1.2
CSSRS		X				X								X				

Procedure	Pre-Treatment Days		Treatment Periods 1 and 2 (Days)								Treatment Period 3 only (Days)							Notes
				Washout								Washout						Hours (h) relate to PK sampling post last dose
	-2	-1	1	2	3 -5	6	9	12	16	17-22	1	2	3-5	6	9	12	16	
VH3739937 Dose Administration			X								X							Randomization to occur on Day 1 prior to dosing. For meal instructions prior to dose, see Section 5.3.1
12-Lead Safety ECGs		X	X			X	X	X	X		X			X	X	X	X	All ECG timepoints on Day 1 in Periods 1-3 will be taken at pre-dose, 2 h and 4 h post dose. Pre-dose ECGs in Periods 1-3 will be taken in triplicate. For further detail, see Section 8.1.4
Plasma PK Sampling			X	X	X	X	X	X	X		X	X	X	X	X	X	X	2mL of blood will be collected at pre-dose (within 15 mins prior to dosing) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 48, 72, 96, 120,192, 264, 360 h post dose. For further detail, see Section 8.4. Please see SRM for details of blood collection and processing.
Haematology/ Chemistry/Urine Test		X		X		X	X	X	X			X		X	X	X	X	Day -1 assessments will be collected prior to dosing periods for all treatment periods. Day 2 samples in each period to be collected 24 h post dose. For further detail, see Appendix 2
SAE review	←==========																==========→	All SAEs will be collected from screening until follow up visit

Procedure	**Pre-Treatment Days**		**Treatment Periods 1 and 2 (Days)**								**Treatment Period 3 only (Days)**							**Notes**
				Washout								**Washout**						Hours (h) relate to PK sampling post last dose
	-2	**-1**	**1**	**2**	**3 -5**	**6**	**9**	**12**	**16**	**17-22**	**1**	**2**	**3-5**	**6**	**9**	**12**	**16**	
AE review			←==========														==========→	All AEs will be collected from first dose until follow up visit
Concomitant medications	←==========																==========→	

2. INTRODUCTION

2.1. Study Rationale

The inhibition of maturation and release of human immunodeficiency virus-1 (HIV-1) is a novel target for drug development, distinct from viral protease, reverse transcriptase and integrase. There are no maturation inhibitors (MI) approved for the treatment of HIV infection. VH3739937 is a MI that displays *in vitro* evidence of low nanomolar potency against multiple HIV-1 Gag polymorphisms and a broad spectrum covering multiple HIV-1 subtypes, supporting compound development. This is a double-blind (sponsor-unblinded), randomised, placebo-controlled, first-time-in-human (FTIH) study in a combined single- and multiple-dose protocol to investigate the safety, tolerability and PK of VH3739937 in healthy participants. This study is designed in three parts: i) to gain information on the safety, tolerability, and pharmacokinetic properties of VH3739937 when administered as powder-in-a-bottle (PiB); ii) the relative bioavailability (RBA) of the GSK3739937 PiB and GSK3739937 Tablet and; iii) to evaluate the safety, tolerability and pharmacokinetic (PK) parameters of the tablet formulation when administered under fasting and fed conditions. This study will enable further clinical development of VH3739937, including a Phase IIA Proof of Concept (PoC) study in HIV-infected patients, a First-Time-in-Human study of the long acting formulation of VH3739937, as well as supporting the future studies of parenteral administration (subcutaneous and intramuscular routes) of a long acting formulation of VH3739937.

2.2. Background

It is estimated that approximately 38 million people are currently living with HIV/Acquired Immunodeficiency Syndrome (AIDS) and that the worldwide epidemic continues to grow at a rate of 1.7 million new infections and cause 770,000 deaths per year [Fact sheet, 2019]. Chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with long term toxicity of anti-retroviral therapy (ART). The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all antiretroviral classes.

Chronic exposure to combination anti-retroviral therapy (cART) has identified anti-retroviral (ARV)-associated long-term toxicities (e.g. central nervous system (CNS) or cardiovascular (CV)/metabolic effects, renal disease, etc.), creating a need to address and prevent these co-morbidities. Regimens which avoid particular classes of agents may help avoid or manage comorbidities among people living with HIV (PLHIV) and the use of 2 drug regimens have the potential to reduce long term toxicities by reducing ARV exposure. Treatment failure remains a continuing concern in clinical care due to the presence and emergence of resistant strains and tolerability issues. In addition, managing an ageing population of PLHIV with an increasing prevalence of comorbidities and polypharmacy requires ARVs with the potential for fewer drug-drug interactions.

VH3739937, an HIV-1 maturation inhibitor (MI) has a novel mechanisms of action (MoA) and has the potential to meet these required characteristics for future therapy.

There is considerable interest in long acting antiretroviral therapy which allow less than daily dosing among PLHIV. Long acting (LA) regimens offer potential advantages over daily oral regimens including less frequent dosing, improved adherence, treatment satisfaction and outcomes.

The inhibition of maturation and release of human immunodeficiency virus-1 (HIV-1) is a novel target for drug development, distinct from viral protease, reverse transcriptase or integrase. There are currently no MIs approved for the treatment of HIV infection. VH3739937 is a MI that displays *in vitro* evidence of low nanomolar potency against multiple HIV-1 Gag polymorphisms and a broad spectrum covering multiple HIV-1 subtypes, supporting compound development and has the potential to be developed as a long acting formulation as well as an oral formulation. It is anticipated the oral version will be used as an oral lead in to establish short term safety and tolerability prior to LA administration or to bridge periods where LA dosing is not possible. The oral version of VH3739937 will support the undertaking of the phase 2a POC study and drug-drug interaction studies.

VH3739937 is a next-generation HIV MI with a similar chemical structure and profile to GSK3640254 which is being developed as an oral ARV. Both MIs have improved profile over prior developmental MIs as they (1) exhibit significantly improved pan-genotypic coverage and potency against polymorphic variants; (2) *in vitro* data suggest that both MIs exhibit a higher barrier to emergence of resistant viruses (except for A364V); (3) both MIs have improved potency *in vitro* toward all HIV-1 subtypes; and (4) it has a projected lower once-daily (QD) human dose. Summaries of the pre-clinical studies are included in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number 2019N421306_00].

2.2.1. Background Key Safety and PK data with Prior Maturation Inhibitors (GSK3532795 and GSK3640254)

Bristol-Myers Squibb (BMS), and later ViiV Healthcare (VH), developed an HIV-1 MI (GSK3532795), which was studied through Phase 2b studies in both treatment-naïve (AI468038) and experienced (AI468048) HIV-1 infected adults. In study AI468038, a greater number of participants who received GSK3532795 experienced gastrointestinal (GI) intolerability (specifically G1-2 diarrhoea and abdominal pain). A detailed examination of all GI AEs (regardless of Grade/Relationship) revealed a relationship with dose [GlaxoSmithKline Document Number 2016N302783_00]. Ultimately, the rate of GI intolerability in the GSK3532795 dose groups in the Phase 2b study AI468038, helped lead to VH's decision to end all clinical trials and not progress to Phase 3 studies.

GI AEs were also previously observed in healthy participants in Phase 1 studies with varying doses, durations, and formulations of GSK3532795. First, in AI468049, the rates of GI AEs ranged from 33-67% across cohorts (single oral doses of GSK3532795 60 mg – 180 mg with food) [GlaxoSmithKline Document Number 2016N297636_00]. Second, in AI468063, 65% of participants receiving GSK3532795 180 mg QD with food

developed diarrhoea [GlaxoSmithKline Document Number 2017N319618_00]. Finally, in AI468052, 29% of participants who received GSK3532795 180 mg once daily (QD) with food developed GI AEs. In all three studies, the most common GI AEs were abdominal pain and diarrhoea.

Aside from mild-moderate GI intolerability, two SAEs occurred in phase I study AI468044 in healthy participants receiving supra-therapeutic doses of GSK3532795: one healthy participant had acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed by a psychiatrist. These two participants received GSK3532795 240 mg twice daily (BID) and 240 mg QD for 3 days with food, respectively. These events were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric AEs in studies with GSK3532795 were headache, dizziness and sleep abnormalities (e.g. insomnia, abnormal dreams) [GlaxoSmithKline Document Number 2017N332341_00].

GSK3640254, was evaluated in a First time in human study (207187) and in a Phase 2a proof of concept study in HIV-1 infected, treatment-naïve patients. Study 207187 was carried out in two parts (Part 1 and Part 2). Participants in Part 1 received single ascending doses of GSK3640254 (1-700 mg) and participants in Part 2 received repeated daily doses of GSK3640254 at different concentrations (50-320 mg)

GSK3640254 did not show any major tolerability findings (including AEs, vital signs, ECG findings, or laboratory values) when given to healthy males in single doses (up to 700 mg) or daily doses (up to 320 mg QD for 14 days), supporting further clinical development of GSK3640254. Three participants from Part 1 and one participant from Part 2 of the study were withdrawn due to adverse events.

GI related AEs were reported in 6 of 16 participants from Part 1 and 13 of 56 participants from Part 2 of the study. All these events were mild in intensity. No dose/AE relationship and no major GI tolerability issues were observed in this study.

Psychiatric AEs were reported in 2 of 16 participants from Part 1 and in 6 of 56 participants from Part 2 of the study. All these events were mild (except 1 event of depression in Part 1 that was moderate in intensity in a participant with history of family stressors prior to study entry) and none were considered related to the study treatment.

Neurologic AE of headache was reported in 6 participants from Part 1 and in 15 participants from Part 2. There were no major GSK3640254 related neuro/psychiatric events observed. None of these events (except 1 in Part 2) were considered related to the study treatment.

Skin tissue disorders AEs, contact dermatitis due to ECG leads were reported in 5 out of 16 participants in Part 1. In Part 2 ,14 out of 56 participants reported skin related AEs, contact dermatitis due to ECG leads n=8, dry skin, eczema nummular, miliaria, pruritus rash and rash maculo-papular. All events were mild in intensity and none was considered related to study treatment. One event lead to study discontinuation (rash maculo-papular).

Though there were a number of participants with ECG abnormalities in both parts of the study, none of these findings were considered clinically significant. There were no

clinically significant arrhythmias reported in either Part 1 or Part 2 of the study. No participants had a QT interval corrected for heart rate according to Fridericia's formula (QTcF) value of >500 msec or an increase from baseline >60 msec. A cardiodynamic evaluation of the multiple ascending dose portion of Study 207187 was undertaken based upon concentration vs change from pre-dose QT interval corrected (QTc) using 12-lead Holter ECGs an analysis by iCardiac/eRT. This indicated a weak relationship between QT prolongation and GSK3640254 plasma concentrations and indicated that an effect on QTcF can be excluded up to GSK3640254 plasma concentration of ~2000 ng/mL[GlaxoSmithKline Document Number 2018N392814_01].

To characterize the population pharmacokinetics of VH3739937 and identify important determinants of variability, a population model was conducted as an alternate analysis approach to characterize the pharmacokinetics and the simulation was implemented to predicted the higher single dose and multiple dose cohort PK profile based on the model. The PK of VH3739937 following oral administration was adequately characterized by a linear one-compartment model with first-order absorption and first-order elimination, and with a dose factor and inter-individual variability on CL/F and on the magnitude of proportional residual error. The simulations for higher single dose 640 and 800 mg, multiple daily dose 50 and 100 mg and the multiple weekly dose 500 mg were conducted to predict the PK profile to obtain the Cmax and AUC for safety cover. More detailed information can be found in the Investigator's Brochure Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025].

2.3. Benefit/Risk Assessment

Based upon pre-clinical studies and clinical studies of prior MIs (GSK3532795 and GSK3640254) the major potential risks are GI intolerability (e.g. abdominal pain and diarrhoea), gastric toxicity (effects on parietal cells and chief cells), prolongation of QTc, skin and subcutaneous tissue disorders (maculopapular rash) and neuropsychiatric safety. A preclinical toxicity finding observed microscopically in stomach (single-cell necrosis of parietal cells) was seen in animals at exposures of VH3739937 that will be tested in this study, however the microscopic finding was minimal and reversible in animals. As noted in Section 2.3.1, the GLP hERG invitro assay showed an atypical response (inhibition (~47%) at 2.306 - 0.231 equivalent to 0.073 µg/mL. This is consistent with the other non-clinical CV data which demonstrated high margin (see Section 2.3.1. for further detail).

In a single-dose study of respiratory function in telemetered rats, VH3739937 resulted in mild reductions in respiratory rate and increased reversible pulmonary resistance. The protocol includes frequent monitoring of vital signs including respiratory rate and brief physical examinations including respiratory examination.

The protocol will exclude potential participants from the study with any pre-existing psychiatric condition or positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered CSSRS. The CSSRS assessment will also be administered by a clinician (or qualified designee) during the on-treatment portion of the MAD only.

Thus, to ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, skin disorders and neuropsychiatric safety), this clinical trial will include healthy adults who will be actively monitored by receiving frequent clinical, ECG, and laboratory evaluations during their participation in the trial.

In addition, consistent with Sponsor guidance for early phase studies, this study will be conducted in a hospital-based clinical research unit with prior experience with first-time-in-human-trials, sufficient overnight facilities and immediate emergency care capabilities.

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 Food and Drug Administration (FDA) and European Medicines Agency (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 and reasonably expected adverse events of VH3739937 may be found in the IB [GlaxoSmithKline Document Number 2019N421306_00] and IB Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [VH3739937]		
Cardiovascular (QT prolongation)	Pre-clinically, VH3739937 • In a definitive in vitro hERG assay, there was no hERG channel tail current inhibition at a concentration of 0.073 µg/mL in a protein free system and there was a flat level of hERG channel inhibition (approximately 46% to 48%) at concentrations of 2.306 µg/mL to 0.231 µg/mL. This response was considered to be atypical and an half maximal inhibitory concentration (IC50) value was not estimated. An in vitro cardiac ventricular wedge assay was negative for effects on QT interval or other ECG changes suggestive of effects on cardiac sodium or calcium channels at concentrations up to 2.5 µg.mL in a protein free system. In a definitive cardiovascular telemetry study in dogs, VH3739937 did not have any effect on electrocardiogram at plasma concentration up to 9.82 µg/mL (1.47 µg/mL free). A pivotal 1 month oral toxicity study in dogs was also negative for ECG changes at exposures up to 39.8 µg/mL (5.6 µg/mL free). Weight of evidence	• Protocol exclusion criteria based on ECG parameters and cardiac medical history. • Participants in the study will have a 24 hour holter monitor and continuous ECGs during treatment; they will also have frequent clinical and vital sign evaluations (see SoA table).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	suggests a low potential for QT prolongation in humans at exposures up to the highest predicted mean maximum observed concentration (Cmax) of 3.76 µg/mL (0.26 µg/mL free). • A cardiodynamic evaluation of the multiple ascending dose portion of study 207187 of GSK3640254 was undertaken based upon concentration vs change from pre-dose QTc using 12-lead Holter ECGs an analysis by iCardiac/eRT. This indicated a weak relationship between QT prolongation and GSK3640254 plasma concentrations and indicated that an effect on QTcF can be excluded up to GSK3640254 plasma concentration of ~2000 ng/mL	
Gastrointestinal intolerability	• Clinical signs indicative of gastrointestinal intolerability (sporadic vomiting and abnormal faeces) occurred mainly in dogs at ≥30 mg/kg/day. • GSK3640254: - Low grade GI adverse effects were observed. The most frequent AEs were	• Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms • Participants in the study will undergo intensive physical exam and laboratory testing. In addition, participants will undergo continuous evaluation for adverse events during their participation in the trial; there are clinical stopping criteria based upon incidence and intensity of treatment-emergent AEs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	abdominal pain and diarrhea in studies of GSK3640254. • GSK3532795: - Of note GI intolerability (predominately abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was evaluated through Phase 2b dosing.	
Gastric toxicity	• Gastric toxicity findings were observed microscopically in stomach of single-cell necrosis of parietal cells and/or chief cells, decreased cellularity of parietal cells and other changes in appearance of chief cells and foveolar cells were present in preclinical species dosed for up to 4 weeks. These findings were reversible.	• Based on preclinical toxicity studies, gastric findings were reversible. Gastric toxicity will be investigated in a phase 2b substudy of GSK3640254
Neurologic/psychiatric safety	• Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. • Psychiatric adverse events were reported infrequently in the FTiH study of GSK3640254 and were of low grade.	• Protocol exclusion criterion based on any pre-existing psychiatric condition (including assessment using the CSSRS) for participants in the study. • Participants in the study will undergo intensive physical exam and laboratory testing. In addition, participants will undergo continuous evaluation for adverse events

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• From a Neurologic and Psychiatric AE summary and PK/pharmacodynamic (PD) analysis for GSK3532795 across all studies mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) • CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration	during their participation in the trial; there are clinical stopping criteria based upon incidence and intensity of treatment-emergent AEs. • Participants will be in house throughout the study to ensure rapid diagnosis and management of any potential event. • Finally, participants in the RBA and FE will have CSSRS assessment at Day -1 and discharge, participants in SAD will have CSSRS assessment at discharge, and participants in the MAD will have assessment via a clinician (or qualified designee) administered CSSRS during the on-treatment portion of the study. In the event of a positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the PI/sub-investigator (SI) will arrange for urgent specialist psychiatric evaluation and management.
Skin and subcutaneous tissue disorders	• Across GSK3640254 clinical trials, AEs leading to discontinuation have included urticaria and maculopapular rash.	• Participants will undergo continuous evaluation for adverse events during their participation in the trial supplemented by the use of physical exams.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Protocol includes individual participant stopping criteria, including: o A grade ≥2 rash with concurrent fever with or without concurrent elevations in liver biochemistry reasonably attributable to dosing with VH3739937, in the opinion of the Investigator.

2.3.2. Benefit Assessment

This is a study in healthy participants; no medical benefit will be derived by participant's participation.

2.3.3. Overall Benefit: Risk Conclusion

Given the preclinical profile of VH3739937, the clinical profile of structurally similar MIs (GSK3532795 and GSK3640254), and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving VH3739937 are low, evaluable, and manageable.

2.3.4. Acute Monitoring in FTIH Studies

Consistent with GlaxoSmithKline (GSK)/VH Guidance and Committee for Medicinal Products for Human Use (CHMP) guidelines for early phase studies, the study will be conducted in an accredited Phase 1 Clinical Research Unit(s) with previous experience with first-time-in-human trials and immediate access to hospital facilities for the treatment of medical emergencies.

There will be continuous medical monitoring during the in-house period for all participants as detailed in the SoA for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of VH3739937 following single, repeated daily, and weekly oral administration in healthy participants (Part 1 & 2) • To assess the safety and tolerability of VH3739937 following single oral administration in healthy participants under fasted or fed (moderate calorie and fat) conditions (Part 3) • To evaluate the relative bioavailability (RBA) of GSK3739937 powder-in-bottle (PiB) versus GSK3739937 Tablet and the effect of food on the PK of GSK3739937 Tablets and GSK3739937 PiB (Part 3)	VH3739937 safety parameters: • Adverse events; post baseline values and changes over time of clinical laboratory evaluations (haematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from pre-dose values (Part 1, 2 & 3) • Derived PK parameters for VH3739937 Part 3 (single dose): $AUC_{(0-24)}$, $AUC_{(0-inf)}$, C_{max}
Secondary	
• To describe the PK profile of VH3739937 following single (Part 1 & 3), repeated	Derived PK parameters for VH3739937:

Objectives	Endpoints
daily and weekly (Part 2) oral administration in healthy participants	• Part 1 (single dose): $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F • Part 2 (repeated once daily [QD] dose): ○ Day 1: $AUC_{(0-24)}$, C_{max}, C_{24}, t_{max}, t_{lag} ○ Day 14 (Cohorts 3 and 4): $AUC_{(0-\tau)}$, C_{max}, $C\tau$, t_{max}, $t_{1/2}$, and CL/F ○ Day 18 (Cohort 5): $AUC_{(0-\tau)}$, C_{max}, $C\tau$, t_{max}, $t_{1/2}$, and CL/F • Part 2 (repeated once weekly [QW] dose: ○ Day 1 (Cohort 6): $AUC_{(0-168)}$, C_{max}, C_{168}, t_{max}, t_{lag} ○ Day 15 (Cohort 6): $AUC_{(0-t)}$, C_{max}, Ct, t_{max}, $t_{1/2}$, and CL/F • Part 3 (single dose): C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F
• To examine dose proportionality following single and repeated doses of VH3739937 (Part 1 & 2)	Derived PK parameters for VH3739937: • Part 1 (single dose): $AUC_{(0-inf)}$, C_{max}. • Part 2 (repeated dose): $AUC_{(0-\tau)}$, C_{max}, $C\tau$
• To predict the accumulation from single dose data (Part 1) and assess accumulation of VH3739937 after repeat doses (Part 2 at steady state)	Accumulation indices for PK parameters for VH3739937: • Part 2 (repeated dose): Observed accumulation ratios: $RAUC_{(0-\tau)}$, $R(C_{max})$, R ($C\tau$)
• To assess time to steady-state of VH3739937 (Part 2)	Derived PK parameters for VH3739937: • Part 2 (repeated dose): ○ Cohorts 3 and 4: Pre-dose concentrations on Day 2-14 ○ Cohort 5: Pre-dose concentrations on Day 2-18
Exploratory	
• To assess the exposure response relationship between VH3739937 and safety parameter, including QTcF following single and repeated administration (Part 1 & 2)	• Change-from-baseline QTcF (ΔQTcF)

Objectives	Endpoints
• To collect plasma and urine samples for analysis of metabolites of VH3739937	• Metabolites of VH3739937 in plasma and urine. The analyses will be conducted and reported separately from this protocol.
• To characterize renal excretion of VH3739937, as data permits	• Urinary recovery of VH3739937 (Ae[0-x]), Ae[0-τ] and Ae[0-t]) and renal clearance (CLr)
• To collect duodenal bile for analysis of metabolites of VH3739937 (Part 2, Cohort 5 only)	• Metabolites of VH3739937 in duodenal bile. The analyses will be conducted and reported separately from this protocol

$AUC_{(0-24)}$ = Area under the plasma concentration time curve from zero (pre-dose) to 24; $AUC_{(0-t)}$ = Area under the plasma concentration time curve from zero (pre-dose) to t; $AUC_{(0-inf)}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-τ) = Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state); C_{max} = Maximum observed concentration; C_{24} = Drug concentration at 24 hours post-dose; C_{last} = last observable concentration; t_{last} = time of last observable concentration; C_{τ} (or C_{trough}) = trough serum concentration; CL/F= Apparent oral clearance; ECG= Electrocardiogram; PiB = powder-in-bottle; $RAUC_{(0-\tau)}$ = Accumulation ratio of area under the concentration-time curve over the dosing interval; $R(C_{max})$ = Ratio of maximum observed concentration; R (Cτ) = Ratio of concentration over the dosing interval; RBA = relative bioavailability; t_{max} = Time of occurrence of C_{max}; $t_{1/2}$ = Apparent terminal phase half-life; t_{lag} = lag time.

Note: The exploratory endpoints may be analyzed upon the clinical development continuation of VH3739937.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 1, double-blind (sponsor-unblinded), randomized, placebo-controlled, single- and repeat-dose escalation study including a weekly oral dose MAD cohort and a RBA and FE cohort to investigate the safety, tolerability and PK of VH3739937 in healthy participants.

As described in Figure 3 below, in Part 1, the proposed dosing schedule is designed to investigate single ascending oral doses of VH3739937 initially in Cohorts 1 and 2. Then, at a suitable cross-over point (described below), Part 2 will involve 4 cohorts of multiple ascending dosing of oral VH3739937 when administered:

- once daily for 14 days (Cohorts 3 and 4);
- once daily for 18 days (Cohort 5); and
- three oral doses administered at weekly intervals over two weeks (Cohort 6) (Figure 3).

In Part 3, the RBA and FE (Cohort 7) will include a randomized, open-label, single dose, 3-period crossover study to compare the RBA of single doses of the GSK3739937 PiB

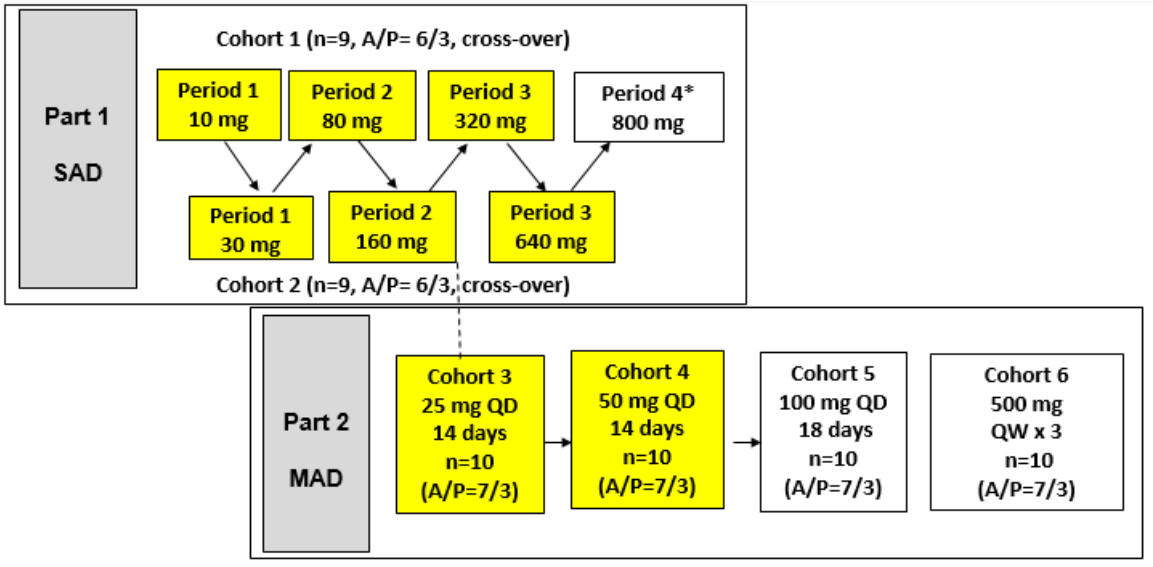
with GSK3739937 Tablet and to assess the effect of food (fasted or fed (under moderate calorie and fat conditions)) upon the safety, tolerability and PK of the GSK3739937 Tablet (Figure 4). All doses will be administered following a standardized meal for each dosing period that contains approximately 600 calories with approximately 30% of calories from fat (unless otherwise indicated in Part 3 dosing in fasted condition).

Overall, approximately 76 participants will be randomly assigned to study intervention. In Part 1, approximately 18 participants will be randomized with approximately 9 participants within each of Cohort 1 and Cohort 2. Part 1 will include an additional higher dose treatment period (800 mg) evaluated in approximately 9 participants as supported by emerging data. In Part 2, approximately 40 participants will be randomized with approximately 10 participants within each of Cohorts 3 to 6. In Part 3, approximately 18 participants will be treated to ensure that 12 evaluable participants complete Cohort 7.

All participants will have a screening visit within 28 days prior to first dose and a follow-up visit approximately 28 days after the last dose. All dosing will be conducted in a hospital based inpatient clinical trial unit. Study participants will be confined to the clinic from Day -2 until discharge. Additional outpatient visits will be required for all study parts. Flexibility of visit scheduling may be required if a pandemic situation applies (see Appendix 7). Otherwise, study assessments will be performed as indicated in the SoA presented in this protocol.

A summary of the overall study design, including proposed doses, sample size, and order, is presented in Figure 3 and Figure 4 below.

Figure 3 Phase 1 Study in Healthy Participants using planned doses of VH3739937 Part 1 and Part 2



A=Active; P=Placebo
QD = once daily; QW = once weekly
*= Period 4 may include participants from both Cohorts 1 and 2
Highlighted cohorts and treatment periods denotes completed

The doses shown in Figure 3 above are intended to demonstrate general concepts relating to factors of escalation. The modelling and simulation implemented using the data currently available following oral administration of a suspension formulation in the fed state indicated the predicted efficacious dose for the daily dose is 25 mg and the weekly dose is 500 mg. Due to the observed half-life of ~90 h, the anticipated accumulation ratio following repeated daily and weekly doses is ~6-fold and 1.3-fold, respectively. Dosing will be conducted in accordance with safety and PK stopping criteria (Section 7.1.4).

In Part 1, dose escalation will be determined by ViiV Healthcare (VH)/GlaxoSmithKline (GSK) study team and the Principal Investigator (PI) and guided by safety data and PK stopping criteria. Post-dose safety and PK data through Day 16 from a minimum of 4 participants receiving VH3739937 are required for dose escalation in Part 1. The suitable crossover point from Part 1 to Part 2 referenced in the above text was determined once the single dose safety and preliminary PK data for the anticipated minimally effective dose was evaluated in Part 1 single ascending dose (SAD) and the maximum exposure for the MAD dose was covered by the SAD certain dose level. In Part 2, Cohorts 3 and 4, dose escalation will be determined by the VH/GSK study team and the PI and guided by the safety and PK data (minimally up to Day 29, 15 days following the Day 14 dose) from the previous dosing Cohort(s). Dose escalation from Cohort 5 will be similarly guided by safety and PK data minimally up to Day 33, 15 days following the Day 18 dose.

Based on human PK predicted from preclinical species, assuming an average bioavailability of ~14% and dose proportionality as well as predicted moderate between-participant PK variability, the highest dose to be assessed in Part 1 was anticipated to be ~640 mg QD. However, as indicated by data evaluated for Part 1 Treatment Periods through 640 mg, VH3739937 exposures are lower than predicted, therefore an additional higher dose SAD treatment period will be evaluated. This higher dose will be conducted in accordance with safety and PK stopping criteria.

Study Design Details Part 1 (SAD):

The SAD portion of the study will be conducted in an interlocking fashion with two separate cohorts each of approximately 9 healthy participants. Each of these two cohorts may contain a minimum of three escalating doses of VH3739937 through to 640 mg. An additional 800 mg dose will be evaluated as this was indicated following review of safety and PK data from participants dosed up to 640 mg. The interlocking design shown in Figure 3 and the randomization sequence in Table 7 will allow the 9 participants in each cohort to potentially receive one of the lower and one of the higher doses of VH3739937. Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses (Table 7). In each escalating dose period, 6 participants will be randomized to receive VH3739937 and 3 participants will be randomized to receive placebo. Participants in either Cohort will be assigned to one of the three treatment sequences, and each participant will receive placebo at least once. When the 800 mg dose is evaluated, 6 participants from both Cohorts 1 and 2 will be randomized to receive VH3739937 and 3 participants will be randomized to receive placebo, independent of which prior doses they received.

Details of the starting dose and dose escalation can be found in Section 4.3

Table 7 Description of treatment sequences in Cohort 1 and Cohort 2 Periods 1, 2, and 3

Cohort 1	Period 1	Period 2	Period 3
Sequence 1	Placebo	Dose 3	Dose 5
Sequence 2	Dose 1	Placebo	Dose 5
Sequence 3	Dose 1	Dose 3	Placebo

Cohort 2	Period 1	Period 2	Period 3
Sequence 1	Placebo	Dose 4	Dose 6
Sequence 2	Dose 2	Placebo	Dose 6
Sequence 3	Dose 2	Dose 4	Placebo

For Part 1, 24-hour continuous Holter/ ECG recordings will be collected on the day before dosing (Day -1), and Day 1 for extraction of ECGs paired with PK sampling.

Participants in Part 1 will have a screening visit within 28 days prior to the first dose and a follow-up visit approximately 28 days after the last dose. Flexibility of visit scheduling may be required if a pandemic situation applies (see Appendix 7). Otherwise, study assessments will be performed as indicated in the SoA. Study participants will be confined to the clinic from Day −2 until discharge. Additional outpatient visits will be required on Days 9, 12 and 16. Duration of study participation in Part 1 may be a minimum of approximately 27 weeks for SAD treatment periods 1 to 3. However, in Part 1, study duration will be extended up to approximately 31 weeks to evaluate a higher dose (800 mg) for participants included in this dose period. Participants who have completed Part 1 may be able to re-enroll to complete 800 mg treatment period. To ensure safety, participants will need to go through re-eligibility assessments.

Part 1 SAD: Dose Escalation

Dose escalation in Part 1 will be determined by the Dose Escalation Committee (VH/GSK study team and the PI) based on the double-blind (sponsor-unblinded) safety data and the PK data from the current and previous dose(s) according to the dose escalation charter. Dose escalation will generally not exceed approximately 3-fold between doses up to approximately the predicted minimally effective dose and will not exceed 2-fold thereafter. However, if after the first SAD dose, the exposures are significantly different from the predicted level, the second dose or the sample collection

schedule will be re-estimated and a different fold increase may be used. Post-dose safety and PK data through Day 16 from a minimum of 4 participants receiving VH3739937 are required for dose escalation in Part 1. Dose escalation will be guided by safety as well as the SAD PK stopping criteria (see Section 7.1.4).

Due to the alternating dosing periods between Cohort 1 and Cohort 2, a participant in either cohort will receive the next dose after approximately 3 or 4 weeks.

Study design details Part 2 (MAD):

Part 2 consists of approximately 4 ascending repeat-dose cohorts (Cohorts 3 to 6), each with 10 participants who will receive a once-daily dose of VH3739937 or placebo (PBO) for 14 days (Cohort 3 [25 mg] and Cohort 4 [50 mg]), or for 18 days (Cohort 5 [100 mg]) or three oral doses at weekly intervals over two weeks (Cohort 6 [500 mg]).

The duration of dosing in Cohort 5 is to support up to 18-day dosing as an oral lead for the future SAD and MAD studies of the long acting formulation of VH3739937. This duration is to allow the identification of any early drug hypersensitivity reactions (HSR) which may occur before the administration of the long acting formulation. In each escalating dose cohort, 7 participants will be randomized to receive VH3739937 and 3 participants will be randomized to receive PBO. Details of the starting dose and dose escalations in Part 2 (MAD) are provided in Section 4.3.

Part 2 of the study was initiated once the single dose safety and preliminary PK data were evaluated in the SAD and the maximum exposure for the first MAD dose was covered by the SAD certain dose level. The potential minimally effective daily oral dose for VH3739937 with the suspension formulation was determined by the modeling and simulation utilising data for all doses in Part 1, as 25 mg, and is anticipated to be that which is predicted to provide a steady state $C\tau \geq 0.258$ μg/mL in 95% of participants. More detailed information may be found in the IB Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025].

Dose escalation in the MAD will not exceed 2-fold between cohorts 3 to 5 and will be driven by safety and PK stopping criteria (see Section 7.1.4). The 500 mg dose included in the MAD Cohort 6 was determined following modeling and simulation of PK data acquired in SAD treatment periods through to 640mg and in MAD Cohort 3. In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1).

For Part 2 MAD Cohorts 3, 4 and 5, 24-hour continuous Holter/ECG recordings will be collected, on the day before the first dose (Day -1), Day 1, and Day 14 for extraction of ECGs paired with PK sampling. In addition, 12-Lead ECGs will be collected for Part 2 at timepoints indicated in the SoA.

Participants in Part 2 will have a screening visit within 28 days prior to first dose and a follow-up visit approximately 28 days after the last dose. Flexibility of visit scheduling may be required if a pandemic situation applies (see Appendix 7). Otherwise, study

assessments will be performed as indicated in SoA. Study participants will be confined to the clinic from Day −2 until discharge with requirement to complete all scheduled outpatient visits. Maximum duration of study participation from admission into the unit until completion of follow visit will be approximately 5 weeks.

Part 2 MAD: Dose Escalation

Dose escalation in Part 2 will be determined by the VH/GSK study team and the PI based on the double-blind (sponsor-unblinded) safety and PK data (minimally up to 15 days following the last dose) from the previous dosing Cohort (s). Specifically, safety and PK data through Day 29 in Cohorts 3 and 4 and through Day 33 in Cohort 5 from a minimum of five participants receiving active drug will be required for dose escalation.

Part 3 (RBA FE)

Part 3 will involve a randomized, open-label, single-dose, 3-period crossover optional Cohort 7 to compare the RBA of the GSK3739937 PiB with GSK3739937 Tablet and to assess the effect of food on the safety, tolerability and PK of GSK3739937 Tablet in healthy participants. In Part 3, approximately 18 participants will be treated to ensure that approximately 12 evaluable participants complete Cohort 7. If participants prematurely discontinue Part 3, additional participants may be randomized after consultation with the sponsor to ensure that approximately 12 evaluable participants complete the study.

Part 3 will consist of a screening period and 3 sequential treatment periods with a single dose of study intervention per treatment period.

Prior to dosing on Day 1 of Period 1, participants will be randomly assigned to 1 of 3 treatment sequences (ABC, BAC, or CAB). Participants will receive each of the following treatments administered as 1 treatment per period:

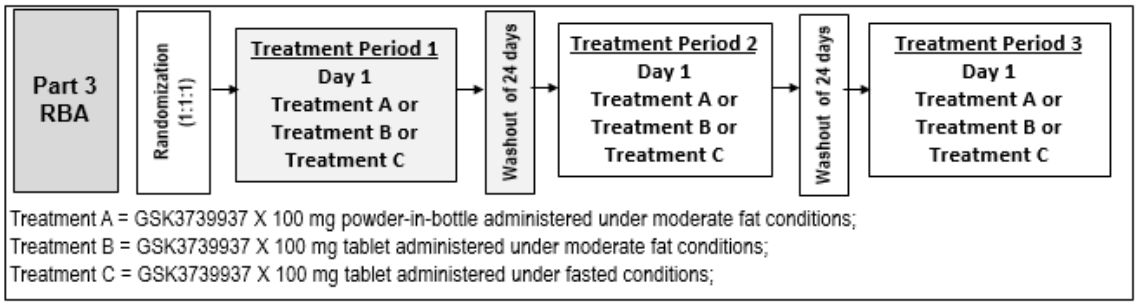
- Treatment A: GSK3739937 PiB, 100 mg (administered as oral suspension) administered under moderate fat conditions (reference)

- Treatment B: GSK3739937 Tablet, 100 mg (single dose given as 100 mg tablet(s)) administered under moderate fat conditions (test)

- Treatment C: GSK3739937 Tablet, 100 mg (single dose given as 100 mg tablet(s))
  administered under fasted conditions (reference).

To ensure adequate washout, there will be at least 24 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 24 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

Figure 4 Phase 1 Study in Healthy Participants using planned doses of VH3739937 Part 3



For treatments administered in the fed state, participants will fast overnight for at least 9.5 hours prior to dosing and will receive a moderate fat (Treatments A and B) meal 25 minutes prior to dosing. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing. Treatment C will be administered in the fasted state. Participants will fast overnight for at least 9.5 hours prior to dosing and until 4 hours after dosing.

Pharmacokinetic blood samples for the analysis of VH3739937 will be collected prior to dosing (0 hour) on Day 1 and up to 360 h hours post-dose in Periods 1, 2, and 3. Additional outpatient visits up to approximately Day 16 post each Treatment A, B and C will be required for collecting necessary PK and safety assessments.

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings.

In Part 3, assessments will be performed as indicated in the SoA. Participants will be confined to the clinic from Day −2 until discharge on Day 6 of each treatment period. Participants are required to complete all outpatient visits during study conduct. Re-admission to the unit will occur on Day -2 for Treatment Periods 2 and 3. A washout period of 24 days is required during treatment periods 1 and 2 prior to dosing in subsequent treatment periods. The duration of Part 3, including Screening, is approximately 16 weeks.

4.2. Scientific Rationale for Study Design

This is a first time in human study that will assess the safety, tolerability, and PK of VH3739937, an HIV-1 MI. The data gathered will inform subsequent clinical trials for VH3739937, including a Phase 2a POC study in HIV-1-infected participants as well as a FTiH study of VH3739937 administered parenterally (subcutaneously or intramuscularly).

All doses of VH3739937 in this study will be administered in the fed state with dosing occurring within 15 minutes of completing a standardized moderate fat meal, unless otherwise indicated in Part 3 Treatment C (i.e. within 5 minutes after completing the

meal). Data with previous MIs, GSK3532795 and GSK3640254, demonstrated that food was necessary to achieve dose proportional PK and target efficacious concentrations (see Section 2.2.1.). Given the structural similarities, including solubility limitations, between GSK3532795, GSK3640254 and VH3739937, administration of VH3739937 with food in this study is expected to enhance both bioavailability and the likelihood for linear PK, allowing for a rigorous assessment of safety and tolerability across a larger exposure range than would be allowed in the fasted state. Finally, VH intends to administer VH3739937 in the fed state in a future Phase 2a POC study in HIV-infected participants; the current study will assess the safety, tolerability, and PK of VH3739937 under the same conditions in healthy participants prior to dosing in HIV-infected participants. The relative bioavailability cohort is planned to assess the impact of the fasted and fed state on VH3739937 bioavailability.

In Part 2 of the study (MAD), doses up to 4 times the minimally anticipated effective dose following oral administration of the suspension formulation (25 mg) are planned to be evaluated in Cohorts 3 to 5 and a higher 500 mg weekly dose will be evaluated in Cohort 6. In future studies in HIV-1-infected participants, these doses/exposures may be evaluated to understand the relationship between VH3739937 exposures and efficacy, duration of response, and resistance development. Furthermore, assessment of this dose/exposure range (anticipated to be the therapeutic exposure range in the target population) in healthy participants will inform safety and tolerability prior to exposing a more vulnerable HIV-1-infected population to VH3739937 and will inform risk mitigation strategies for potential drug interactions.

This dose/exposure range in healthy participants is clinically reasonable based upon the preclinical profile of VH3739937 and the clinical profile of prior MIs (GSK3640254 and GSK3532795), and the planned inpatient and outpatient evaluation for potential treatment emergent risks: including QT prolongation, GI intolerability and neuropsychiatric safety – which will be frequently monitored in this limited dosing duration setting. The preliminary data observed to date in this study (212548) through 640 mg in the SAD and 25 mg QD for 14 days in the MAD have not highlighted a significant safety concern. Phase 1-2a studies with GSK3640254 have not evaluated for the presence of gastric toxicity in humans; thus, it is unclear if any of the GI AEs observed in any clinical trial were representative of, associated with, or resulted from gastric toxicity (if present). However, a currently active Phase 2b study of GSK3640254 includes a sub-study to assess the potential for GI toxicity.

4.3. Justification for Dose

4.3.1. Predicted Human Pharmacokinetics

The pharmacokinetic profile for VH3739937 in humans was predicted using allometric scaling across all species (mouse, rat, dog, and monkey), and was combined with Css-MRT modeling to obtain the predicted human PK profile [GlaxoSmithKline Document Number 2020N427033_00]. Using this method, the intravenous (IV) plasma clearance in humans for VH3739937 is projected to be low (0.12 mL/min/kg) and the intravenous volume of distribution was predicted to be 0.25 L/kg. The elimination half-life was

anticipated to be around 24 hours, leading to an approximate 2-fold anticipated accumulation with once daily dosing. The mean oral bioavailability in animals was approximately 12% (based on simultaneous fitting of the IV and oral animal data using compartmental modeling) and assumed for exposure projections in humans.

4.3.2. Predicted Human Effective Dose

Trough concentrations (Cτ) are typically the PK parameter of interest for efficacy for other antiretroviral classes such as protease inhibitors and integrase inhibitors. The target Cτ for VH3739937 was established using the average of 3-times the protein binding-adjusted EC_{90} (3xPBA-EC_{90}) for a small library of 6 Gag/Pr genotyped viruses less sensitive to a precursor maturation inhibitor GSK3640254. These viruses exhibited an average 3xPBA-EC90 of 312 nM (0.258 μg/mL). A similar 3xPBA-EC90 value was observed towards Δ370 virus (309 nM). The predicted dose that achieves a Cτ at steady-state ≥ target concentration in ~ 95% of the simulated subjects will be selected as the minimal effective dose.

Prior to study initiation, the rationale for estimation of the minimally effective dose and associated PK parameters was as follows:

The potential minimal effective dose for VH3739937 was estimated using the predicted human PK profile, assuming 50% between subject variability (IIV) on CL, V2 and Ka, the same parameters for which moderate to high IIV was estimated in a preliminary population PK model for GSK3640254, based on data from a FTIH study profile [GlaxoSmithKline Document Number 2020N427033_00]. This led to the prediction of a likely minimally effective once daily dose of approximately 80 mg. At this dose, the mean repeat-dose Cmax is predicted to be approximately 0.94 μg/mL, mean Cτ is predicted to be approximately 0.68 μg/mL and mean AUC is predicted to be approximately 20.1 μg*h/mL (Table 10). The anticipated steady-state mean AUC is 1.27-fold lower than the no observed adverse effect level (NOAEL) in the rat (25.5 μg*h/mL), 4.79-fold lower than the lowest observed adverse effect level (LOAEL) in the rat (96.2 μg*h/mL), and 2.58-fold lower than the LOAEL in the dog (51.9 μg*h/mL).

However, during the course of study 212548 conduct, modelling and simulation of PK data from SAD treatment Periods 10 mg, 30 mg, 80 mg, 160 mg, 320 mg and 640 mg have led to the revision of the estimation of the predicted minimally effective dose and associated PK parameters. More detailed information may be found in the IB Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025].

4.3.3. Part 1 (SAD) Starting Dose and Dose Escalation

The starting oral dose of VH3739937 in the SAD will be 10 mg. Assuming a 10-fold safety factor and a body weight of 70 kg, this starting dose is lower than that calculated based on the NOAEL in rat of 10 mg/kg/day (maximum recommended starting dose [MRSD] = 11.3 mg) and the LOAEL in dog of 3 mg/kg (MRSD = 11.7 mg), in the absence of a NOAEL in dog [FDA/CDER, 2005]. Although a NOAEL was not established in the 4-week dog study due to the presence of gastric toxicity at all doses, the gastric findings at 3 mg/kg/day (LOAEL) were minimal in severity and reversible.

Based on the predicted human PK, a 10 mg dose would provide a mean AUC(0-inf) of 2.58 µg*h/mL and a mean Cmax of 0.0454 µg/mL. This predicted AUC(0-inf) is ~10-fold lower than that observed in the rat at the NOAEL (25.5 µg*h/mL), 20.1-fold lower than that observed in the dog at the LOAEL (51.9 µg*h/mL), and 37.3-fold lower than that observed in the rat LOAEL (96.2 µg*h/mL).

Dose escalations in Part 1 (SAD) will be governed in real-time by safety and PK stopping criteria (see Section 7.1.4. and Section 7.1.5). Based on the assumptions described above, the top dose anticipated in Part 1 was a single dose of 640 mg. However, following review and evaluation of emerging available PK and safety data, a higher SAD dose of 800 mg was selected for evaluation in Cohort 1, Period 4. Observed exposures were lower than that projected and review of preliminary safety data from the SAD 10mg through to 640mg dose and the MAD 25mg dose, supported escalation to the 800mg dose. These preliminary PK and safety data are summarised in the IB Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025]. The predicted median Cmax for 800 mg dose was 1.60 µg/mL. This higher 800mg dose will be in accordance with SAD PK stopping criteria. Based on the data collected from the observed doses so far in the study, the probability of any SAD participant having a Cmax > 21 µg/mL is extremely low.

4.3.4. Part 2 (MAD) Starting Dose and Dose Escalation

The initial dose in the MAD (Cohort 3) was approximately equal to the likely minimally effective dose, re-estimated at 25 mg based on the clinical PK data following oral administration of the suspension formulation collected in the early doses of Part 1. Dose escalation in the MAD will not exceed 2-fold between daily dosing cohorts 4 and 5 and will be governed by both safety and MAD PK stopping criteria (see Section 7.1.4 and Section 7.1.5). Based on emerging PK data in Part 1, the once weekly (QW) dosing Cohort 6 will be dosed at 500 mg. Given different assumptions for the between participant AUC variability (%CVb) and the current human PK prediction, the probability of any participant AUC(0-τ) in the MAD above 96.2 µg/mL, the LOAEL exposure in rat, are illustrated in Table 8. Similarly, the probability of any participant AUC(0-24) which cover the maximum exposure in the MAD Cohort 6 above 96.2 mg/mL is illustrated in Table 9.

Table 8 Probability of any MAD participant (AUC(0-τ) >96.2 µg*h/mL) for potential QD doses

AUC variability	Potential VH3739937 QD MAD Doses		
%CVb[1]	25 mg	50 mg	100 mg
25	0	0	<0.001
35	0	0	0.003
50	0	<0.001	0.028

Note: 1, %CVb: between-participant coefficient of variation

Table 9 Probability of any MAD participant (AUC(0-τ) >96.2 µg*h/mL and (Cmax >21 µg/mL)) for 500 mg QW dose

AUC variability (%CVb[1])	Cmax Variability (%CVb[1])	Any Participant (AUC >96.2 µg*h/mL or Cmax >21 µg/mL)
25	25	0

Note: 1, %CVb: between-participant coefficient of variation

Given the results in the tables above, it is unlikely that any subject exceeds the safety thresholds in the QD or QW MAD portions of the study.

4.3.5. Part 3 RBA Dose Selection

The relative bioavailability of a 100 mg tablet formulation will be assessed in Part 3, using the PiB formulation as a reference. A 100 mg unit tablet dose was chosen as a reasonable representative dose for this assessment, given available PiB pharmacokinetic data and projected clinical doses (25 mg QD or 500 mg QW).

Although no definitive preclinical data on solid dose bioavailability is available, it is unlikely that moving to a tablet will result in significantly higher exposure (as Cmax or AUC) relative to a 100 mg PiB dose. Given doses of up to 640 mg PIB have been safely administered in Part 1, there is no perceived safety risk.

4.3.6. Dose Escalation Committee (DEC)

This study will utilize a dose escalation committee made up of at least the following: Sponsor and Site staff (including safety physicians and clinicians, PI, Sub-Investigator, Medical Monitor, clinical pharmacokineticist/pharmacologist, data manager, pharmacovigilance, and statistician) and/or their delegates. The committee will evaluate data including but not limited to: AEs, vital signs, laboratory findings, ECG parameters, and PK data. The DEC will meet when data are available from a minimum of 4 active treated participants through Day 16 assessments in Part 1, and from a minimum of 5 active treated participants through Day 29 assessments in Part 2 Cohorts 3 and 4, and similarly through Day 33 assessments in Cohort 5. A dose escalation plan will document the structure and function of the DEC. This plan is included in the Dose Escalation Charter which will also specify the safety and PK requirements for the DEC prior to making a dose escalation decision. The blinding of personnel is discussed in Section 6.4.

4.3.7. Anticipated Exposure and Safety Cover for a Range of Potential Doses

Projected steady-state exposures of GSK3739937 from potential doses in Part 2 are compared to target efficacious concentrations and preclinical toxicity exposures in Table 10. Projected steady-state PK for a range of potential QD (50-100 mg) or QW (500 mg) doses following fed administration and comparison to efficacy target and preclinical exposure in Table 11. Predicted human exposure following multiple doses can be compared to the NOAEL and LOAEL in rats, the Cmax from the dog CV study and to LOAEL in dogs. Findings in both species were GI related, limited and reversible (see

Section 2.3.1 and the Clinical Investor Brochure [GlaxoSmithKline Document Number 2019N421306_00] for further details).

Importantly, the doses listed here are intended to demonstrate general concepts relating to factors of escalation. The specific doses in the SAD and MAD portions are subject to change based upon emerging clinical and PK data gathered in this study. As described above, dose escalations will be governed in real-time by safety and PK. A dose which has met formal clinical, QT, and PK stopping criteria (see Section 7) will not be repeated in the SAD or MAD.

Table 10 Projected steady-state PK for a range of potential QD doses following fed administration and comparison to efficacy target and preclinical exposure

Parameter	10 mg	30 mg	80 mg	160 mg	320 mg
Cτ, µg/mL					
Mean	0.085	0.255	0.68	1.36	2.72
Lower bound of 90% CI	0.036	0.107	0.28	0.57	1.14
Cτ/Ctarget (0.258 µg/mL)					
Lower bound of 90% CI	0.140	0.421	1.12	2.24	4.49
Cmax Day 14, µg/mL					
Mean	0.117	0.352	0.939	1.88	3.76
Upper bound of 80% CI [a]	0.207	0.620	1.65	3.31	6.61
Cmax Cover with[b]					
Dog 1-month GLP study (39.8 µg/mL)[c]	729	242	90.8	45.4	22.7
Dog CV study (9.82 µg/mL)[d]	180	59.8	22.4	11.2	5.60
Mean AUC, µg*h/mL					
Mean	2.51	7.52	20.1	40.1	80.2
Upper bound of 80% CI [a]	4.63	13.9	37.0	74.1	148
AUC Cover with[b]					
Rat NOAEL (25.5 µg*h/mL)	10.16	3.39	1.27	0.636	0.318
Rat LOAEL (96.2 µg/mL)	38.3	12.8	4.79	2.40	1.20
Dog LOAEL (51.9 µg/mL)	20.7	6.90	2.58	1.29	0.647

a. The upper bound of the 80% CI is presented to capture the likely highest PK values in 6 subjects.
b. The Cmax and AUC cover were computed as the ratio of Cmax or AUC in animal divided by the mean Cmax or AUC predicted in human.
c. Equivalent to 85.3 µg/mL in human (based on 85% and 93% protein binding in dog and human, respectively).
d. Equivalent to 21.0 µg/mL in human (based on 85% and 93% protein binding in dog and human, respectively).

Table 11 Projected steady-state PK for a range of potential QD (50-100 mg) or QW 500 mg) doses following fed administration and comparison to efficacy target and preclinical exposure

Parameter	50 mg	100 mg	500[e] mg
Cτ, µg/mL			
Median	0.905	1.57	0.429
Lower bound of 90% CI	0.557	1.01	0.253
Cτ/Ctarget (0.258 µg/mL)			
Lower bound of 90% CI	2.16	3.91	0.981
Cmax after last dose, µg/mL			
Median	0.968	1.72	1.5
Upper bound of 90% CI[a]	1.53	2.65	2.07
Cmax Cover with[b]			
Dog 1-month GLP study (39.8 µg/mL)[c]	88.1	49.6	58.8
Dog CV study (9.82 µg/mL)[d]	21.7	12.2	14.5
Mean AUC, µg*h/mL			
Median	22.7	39.8	31.3
Upper bound of 90% CI[a]	36.1	62.0	45.5
AUC Cover with[b]			
Rat NOAEL (25.5 µg*h/mL)	1.12	0.641	0.815
Rat LOAEL (96.2 µg/mL)	4.24	2.42	3.07
Dog LOAEL (51.9 µg/mL)	2.29	1.30	1.66

a. The upper bound of the 95% PI is presented to capture the likely highest PK values.
b. The Cmax and AUC cover were computed as the ratio of Cmax or AUC in animal divided by the median Cmax or AUC predicted in human.
c. Equivalent to 85.3 µg/mL in human (based on 85% and 93% protein binding in dog and human, respectively).
d. Equivalent to 21.0 µg/mL in human (based on 85% and 93% protein binding in dog and human, respectively).
e. The weekly dose 500 mg
f. the maximum 24 hour AUC were calculated from 0-24h after the last dose to match the daily safety limit 96.2 ug*h/mL

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit and the last scheduled procedure shown in the SoA

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

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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 AND DISEASE CHARACTERISICS
2. Participants who are overtly healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG). 3. Participants who are negative on two consecutive tests for SARs-CoV-2, performed at Screening, on admission and (re-)admission to the Phase I unit, using an approved molecular test (PCR). 4. Participants who are able to understand and comply with protocol requirements and timetables, instructions, and protocol-stated restrictions.

WEIGHT
5. Body weight ≥50.0 kg (110 lbs.) for men and ≥45.0 kg (99 lbs) for women and body mass index within the range 18.5 to 32.0 kg/m^2 (inclusive).

SEX
6. Male and/or female **Male participants:** Male participants are eligible to participate if they agree to the following during the intervention period and for at least 5 days, corresponding to time needed to eliminate study intervention(s) (e.g. 5 terminal half-lives) plus an additional 90 days (a spermatogenesis cycle) after the last dose of study intervention: • Refrain from donating sperm PLUS either: • Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use a male condom

  AND

  And female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4

  OR

  And should also be advised of the benefit for a female partner 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

- Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

Female participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and is not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

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
7. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (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. 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
2. Contact with known COVID-19 positive person/s in the 14 days prior to inpatient admission
3. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, distribution, metabolism, or elimination of drugs;

constituting a risk when taking the study intervention or interfering with the interpretation of data

4. Pre-existing clinically relevant, in the opinion of the PI, gastro-intestinal pathology or diagnosis – e.g. irritable bowel syndrome, inflammatory bowel disease, and/or significant baseline signs and symptoms.
5. Medical history of cardiac arrhythmias or cardiac disease or a family and personal history of long QT syndrome.
6. Any known or suspected pre-existing psychiatric condition
7. Any positive (abnormal) response confirmed by the investigator or clinician (or qualified designee) administered CSSRS at screening
8. Any other clinical condition (including but not limited to active substance use) or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study; unable to comply with dosing requirements; or unable to comply with study visits; or a condition that could affect the absorption, distribution, metabolism or excretion of the drug.
9. Estimated Glomerular Filtration Rate (eGFR) <90 mL/min or serum creatinine >1.1 x ULN.
10. Hemoglobin <12.5 g/dL for men and <11 g/dL for women
11. Alanine transaminase (ALT) or aspartate aminotransferase (AST) >1.1x upper limit of normal (ULN)
12. Bilirubin >1.1xULN (isolated bilirubin >1.1xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
13. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
14. Any significant arrhythmia or ECG finding (e.g., prior myocardial infarction in the past 3 months (does not include ST segment changes associated with re-polarization), symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats), second-degree atrioventricular block Mobitz Type II, third-degree atrioventricular block, complete heart block, or conduction abnormality (including but not specific to left or right complete bundle branch; AV block [2nd degree or higher]; WPW syndrome), Sinus Pauses > 3 seconds, which, in the opinion of the investigator or VH/GSK Medical Monitor, will interfere with the safety for the individual participant.
15. Exclusion criteria for Screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 or >100 bpm	<50 or >100 bpm
PR interval	<120 or >220 msec	
QRS duration	<70 or >120 msec	
QTcF interval	>450 msec	

Note:

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

- The QTc is the QT interval corrected for heart rate according to QTcF, and/or another method, machine-read or manually over-read.
- The specific formula that will be used to determine eligibility and discontinuation for an individual subject will be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

PRIOR/CONCOMITANT THERAPY

16. 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, such as paracetamol listed in Section 6.6 may be allowed].
17. Unwillingness to abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos within 7 days prior to the first dose of study treatment(s) or until the end of the study.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

18. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days
19. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
20. Current enrolment or past participation within the last 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) before signing of consent in this or any other clinical study involving an investigational study intervention or any other type of medical research

DIAGNOSTIC ASSESSMENTS

21. Presence of HBsAg at screening or within 3 months prior to first dose of study intervention
22. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C Ribonucleic acid (RNA) test is obtained
23. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention
NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
24. Positive pre-study drug/alcohol screen
25. Positive HIV antibody/antigen test
26. Regular use of known drugs of abuse
OTHER EXCLUSIONS
27. 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.
28. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening and at admission.
29. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or 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 their fruit juices within 7 days before the start of study intervention until the end of the study.
- In Part 1 and 2, participants will refrain from water intake between 1-hour pre and 1-hour post dosing. No water intake restrictions at other times.
- All doses of VH3739937 in Part 1, Part 2, and Part 3 (Treatments A and B only) in this study will be administered in the fed state (moderate fat). The participants in Part 1, Part 2 and Part 3 (Treatments A and B) will fast for at least 9.5 hours prior to dosing and will receive a standardized moderate fat meal 25 minutes prior to dosing. Participants will eat this meal in up to 25 minutes with dose administration to occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours post-dose. The standardized moderate fat meal will contain about 600 calories with approximately 30% of them coming from fat.

- Meal times should be approximately uniform across all treatment periods. The food content of meals must be identical on serial PK sampling days. At all other times, meals will follow site usual practice.
- The participants in Part 3 (Treatment C) will be administered study intervention in the fasted state. The participants will fast overnight for at least 9.5 hours prior to dosing and until 4 hours after dosing. No water is allowed from 2 hours prior to dosing until 2 hours after dosing except for the glass of water needed to administer the study medication (e.g. 240 mL). Water is allowed ad libitum at all other times.
- In MAD Cohort 5 Day 18 only, participants will undergo biliary metabolism testing using the Enterotest or EnteroTracker for analysis of VH3739937 and its metabolites. The duodenal bile sample collected from placebo-dosed participants in this same cohort will be considered as the control sample. The string as a capsule device will be swallowed by fasted participants at approximately 2 hours after dosing on Day 18 of dosing and removed at approximately 6.5 hours post dose.
- Additional details on the Bile Sample Collection, Food Cue, EnteroTest or EnteroTrack placement, bile sample storage and shipment procedures can be found in the study reference manual (SRM).

5.3.2. Caffeine, Alcohol, and Tobacco

- 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 until after collection of the final PK and/or pharmacodynamic sample.
- Use of alcohol or tobacco products will not be allowed from screening until after the final follow-up visit.
- Participants must have a negative drug test at screening and admission to the clinical unit and must abstain from recreational drug use from screening until after the final follow-up visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 24 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

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

Participants in a pandemic situation who meet all eligibility criteria at screening but no longer remain within the screening window prior to study admission on Day -2, may have all screening procedures repeated (see Appendix 7). In this situation rescreened participants should be assigned a new participant number from that assigned at the initial screening.

6. STUDY INTERVENTION

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 investigation interventions used in study 212548 are GSK3733937 Powder in bottle (PiB) and GSK3733937 Tablet, 100 mg (can also be referred to as VH3733973 PiB and VH 3739937 Tablet, 100 mg)

6.1. Study Intervention(s) Administered

Intervention Name	GSK3739937 Powder-in-Bottle (PiB)	Placebo for GSK3739937 PiB	GSK3739937 Tablet[1]
Dose Formulation	Powder-in-bottle for reconstitution with 50 mL of vehicle (0.5% Hypromellose in Sterile Water for Irrigation)	50 mL of vehicle (0.5% Hypromellose in Sterile Water for Irrigation)	Tablet
Unit Dose Strength(s)	Oral Suspension of VH3739937	N/A	100 mg tablet
Route of Administration	Oral	Oral	Oral
Dosing Instructions	Each dose to be reconstituted with 50 mL vehicle followed by additional rinses with vehicle/Sterile Water for Irrigation. The maximum volume of vehicle will not exceed 120 mL/daily. The volume of vehicle / Sterile Water for irrigation rinses will vary across the GSK3739937 doses, volume of vehicle / Sterile water for irrigation for the placebo will also vary to match that of the GSK3739937 dose. Further detail can be found in the SRM.	50 mL of vehicle followed by additional vehicle/Sterile Water for Irrigation rinses. The maximum volume of vehicle will not exceed 120 mL/daily. The volume of vehicle / Sterile Water for irrigation rinses will vary across the GSK3739937 doses, volume of vehicle / Sterile water for irrigation for the placebo will also vary to match that of the GSK3739937 dose. Further detail can be found in the SRM.	Study intervention will be administered by the study personnel during each dosing day with 240 ml of water
Sourcing	GSK3739937 provided as Bulk Powder and Hypromellose	Hypromellose provided centrally by the Sponsor,	Provided in bulk by the Sponsor

	provided centrally by the Sponsor. Sterile Water for irrigation provided by the site	Sterile Water for irrigation provided by the site	
Packaging and Labeling	Study Intervention will be provided in amber glass bottle. Each bottle will be covered to obscure the appearance of the study intervention. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in amber glass bottle. Each bottle will be covered to obscure the appearance of the study intervention. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in bulk by Sponsor. The investigator will package in high-density polyethylene bottles. Each bottle will be labelled as required per country requirement".

[1]Use of GSK3739937 Tablet will be in Part 3, RBA and FE Cohort 7 only

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. Further guidance can be found in the SRM.
- An unblinded pharmacist or designee will prepare blinded study intervention and provide to authorize study staff for administration. Each bottle will be covered to obscure the appearance of the study intervention. The blinded drug product and placebo will be administered by site staff not involved with assessments. For details of the blinding approach refer to the SRM.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the Study Sponsor Medical Monitor and/or Sponsor study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the randomization schedules generated by the Sponsor or their delegate, prior to the start of the study, using the GSK validated randomization software RANDALL NG. Randomization and study treatment assignment will be facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG) for Part 1 Cohorts 1 and 2, treatment periods 1, 2 and 3, and Part 2 Cohorts 3, 4 and 5. Each participant scheduled to receive study intervention will receive a treatment allocation number when randomized. For Part 1, higher dose SAD (800 mg) Treatment Period 4, Part 2 MAD Cohort 6, and Part 3 RBA and FE, RAMOS NG will not be used (see Section 6.4 for additional details).

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

6.4. Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized in a 2:1 ratio to receive study treatment (VH3739937 active drug:placebo) within Part 1 and in a 7:3 ratio in Part 2. Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses). Participants in either Cohort will be assigned to one of the three treatment sequences, and each participant will receive placebo once. In SAD treatment period 4 (800 mg), 6 participants will be randomized to receive VH3739937 and 3 participants will be randomized to receive placebo, independent of which prior doses they received. Investigators unless specified above will remain blinded to each participant's assigned study treatment throughout the course of the study. Part 3, the RBA and FE Cohort 7, will be open label and all 12 evaluable participants will receive VH3739937.

Part 1 and Part 2 will be a double-blind study with participants and the site staff blinded with the following exception: due to the different appearance of VH3739937 PiB and placebo for VH3739937 PiB; an unblinded pharmacist at the site who will prepare the blinded drug product and blinded placebo. The blinded drug product and placebo will be administered by designated unblinded site staff who must not be involved with assessments. The sponsor will be unblinded. For dose escalation, the Sponsor study team physicians, statistician, and clinical pharmacokinetic staff and/or their delegate will have access to unblinded data. The Sponsor will present data at DEC meetings in a blinded fashion when interacting with site staff. Other Sponsor staff will remain blinded unless unblinding becomes 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 CRF, as applicable. The RAMOS NG system will be programmed with blind-breaking instructions for Part 1

Cohorts 1 and 2, treatment periods 1, 2 and 3 and Part 2 Cohorts 3, 4 and 5 in case of an emergency.

For Part 1, higher dose SAD (800 mg dose), Part 2 Cohort 6, and Part 3 RBA and FE Cohort 7, RAMOS NG will not be used. A paper randomization list will be electronically sent to the unblinded site pharmacist or designee by GSK study statistician prior to Day 1 to permit sufficient time for pharmacy to prepare study intervention in advance. Access to randomization codes is limited to only those authorized by unblinded site pharmacist in order to maintain the integrity of the treatment blind. The pharmacy has restricted access and can only be accessible to authorized personnel. The randomization list is stored on a password protected computer or a restricted access pharmacy. The unblinded study monitor will confirm that codes are securely kept locked in a limited access area to preserve the integrity of the treatment blind prior to site initiation. GSK no longer has the capability to support generation of individual randomization envelopes for studies and therefore an alternative strategy will be employed to maintain investigator blinding for higher dose SAD (800 mg), Part 2 Cohort 6, and Part 3 RBA and FE Cohort 7. Upon receipt, the copy of the randomization list per cohort will be transferred to a locked cabinet at the nurses' station. In the event of emergency unblinding, a member of the Parexel staff will retrieve and open the random list for the cohort and unblind the specific participant without revealing any further unblinding information to study staff. The unblinding staff shall be prohibited from working on the study.

The unblinded study monitor will confirm unblinded site staff will maintain study documentation that would unblind the blinded site staff in a separate, limited access location. The unblinded study monitors will ensure that any essential documents containing information that could potentially reveal the blind (ie., IP Accountability, Reconciliation, and Destruction Form) are maintained in a limited access location on site until they can be combined with the sponsor TMF for archiving.

Unblinded monitors, and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

A participant will be withdrawn if the participant's treatment 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.

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

Any instance of unblinding will be documented in the study TMF.

6.5. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested. Participants will not be allowed to use the bathroom at least 1hr after dose.

6.6. Concomitant Therapy

Participants must abstain from taking prescription or non-prescription drugs (including Cytochrome P450 (CYP) inducers and inhibitors, vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Permitted Medications are as follows:

- Paracetamol/Acetaminophen, at doses of ≤2 grams/day, is permitted for use at 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 medication 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 and recorded along with:

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

The Medical Monitor will be contacted if there are any questions regarding concomitant or prior therapy.

6.7. Dose Modification

The decision to proceed to the next dose level in both Part 1 (SAD) and Part 2 (MAD) will be made by the DEC, based on safety, tolerability, and preliminary PK data obtained from the prior dose level(s) as described in the Dose Escalation Committee Charter. Criteria for discontinuation of dose escalation also apply to discontinuation of dosing within the cohort in which a toxicity occurs.

6.8. Intervention after the End of the Study

Since only healthy participants are eligible for study participation, no additional treatment from Sponsor, including VH3739937, will be provided after the completion of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant may be withdrawn from the study at any time:

- At his or her own request
- At the discretion of the Investigator in consultation with the Study Sponsor Medical Monitor for safety (including lab abnormalities or intercurrent illness), psychiatric, compliance, or administrative reasons.
- Emergence of any positive (abnormal) response confirmed by the investigator or a clinician (or qualified designee) administered CSSRS during the on-treatment phase (MAD only).
- ≥ Grade 3 AE (or clinically significant laboratory abnormality) suspected to be related to VH3739937
- A SAE, regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with VH3739937, in the opinion of the Investigator.
- A grade ≥2 rash with concurrent fever with or without concurrent elevations in liver biochemistry reasonably attributable to dosing with VH3739937, in the opinion of the Investigator.
- Termination of the study by the Sponsor. Safety data will be reviewed by the Sponsor in-stream by single case and collectively. If a safety concerns arises, a decision about continuation of the study will be made.
- Loss of ability to freely provide consent due to incarceration or involuntary treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding of unauthorized Site Staff, including the PI, for any reason

- Repeat non-adherence by the participant with the requirements of the protocol or treatment (as determined by Investigator in consultation with the Study Sponsor Medical Monitor)
- Pregnancy (Section 10.4.3)
- PK stopping criteria is met (Section 7.1.4)
- Clinical criteria for stopping study is met (Section 7.1.5)

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.

If a participant chooses to withdraw from the study, he/she will complete a follow-up visit as per SoA.

7.1.1. Liver Chemistry Stopping Criteria

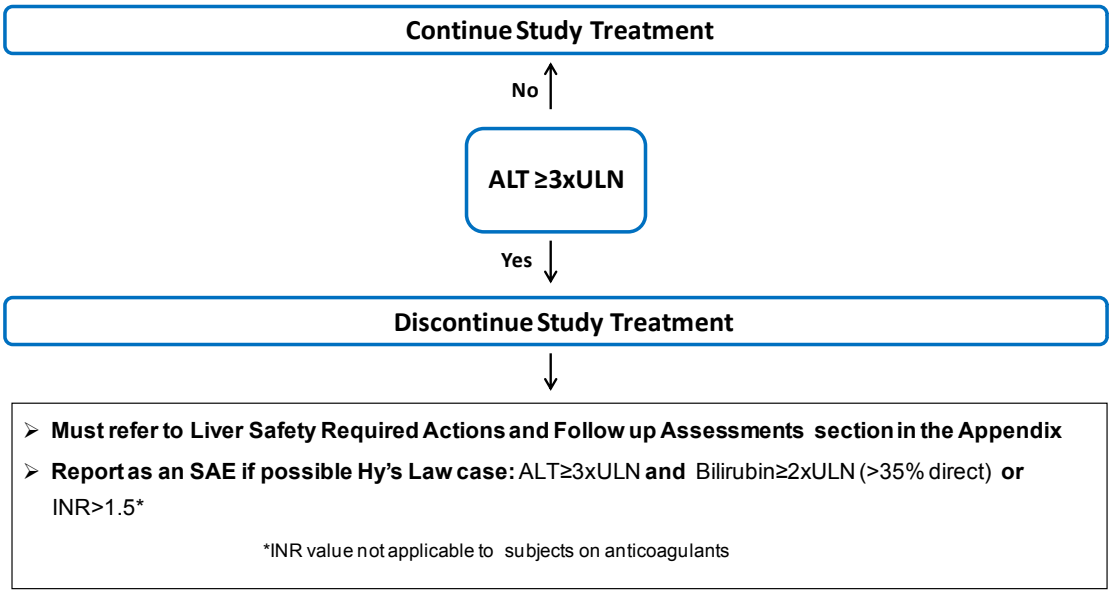
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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

- A participant meets one of the conditions outlined in Figure 5 below.
- When in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

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

Figure 5 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

Details of Liver Safety Required Actions and Follow-Up Assessments can be found in Appendix 5.

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

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

7.1.2. QTc Stopping Criteria

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

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

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

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

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

7.1.3. Temporary Discontinuation

Temporary discontinuation in this study is not allowed.

7.1.4. PK Stopping Criteria for SAD and MAD

In the SAD, the PK stopping criteria are based on mitigating any potential for Cmax mediated effects on ECG parameters. There were no ECG or other CV effects in a good laboratory practice (GLP) single-dose CV study in telemeterized dogs (Cmax = 9.82 µg/mL) and a 1-month GLP study in dogs (Cmax = 39.8). The stopping criteria is conservatively based on lower Cmax in the CV study in telemeterized dogs where there were no CV effects (9.82 µg/mL), equivalent to 21 µg/mL, when adjusted for protein binding. Protein binding is higher in human (93%) compared to dog (85%). If safety or PK stopping criteria are not met for the current/prior doses, dose escalation in Part 1 (SAD) will be stopped in the event that the Bayesian predicted probability is >50% that any participant's Cmax for the next subsequent dose will exceed 21 µg/mL (the SAD PK stopping criteria).

In the MAD, the PK stopping criteria are based on AUC exposures where VH3739937-related microscopic findings were observed in the stomach of rats and dogs in the GLP 1-month oral toxicity studies. Corresponding Cmax exposures are expected to be below 21 µg/mL. A NOAEL was identified for microscopic findings in the stomach of rats at 10 mg/kg/day and a LOAEL in rats was identified at 40 mg/kg/day. A NOAEL for microscopic findings in the stomach of dogs was not identified and the LOAEL in dogs was 3 mg/kg/day. At the LOAEL in rats and dogs, VH3739937 was well tolerated and resulted in minimal, reversible single cell necrosis of parietal cells and chief cells. Exposure at the LOAEL in rats was AUC = 96.2 ug*h/mL and in the dog was AUC = 51.9 µg*h/mL. The LOAEL in rats was chosen as the PK stopping criteria, and exposure is approximately 4-fold higher than the AUC in rats at the NOAEL dose of 10 mg/kg/day. The selection of the higher LOAEL AUC from the two preclinical species arises from the need to achieve sufficiently high exposures for cardiodynamic assessment of the TQT prolongation risk and mitigate the need for a TQT study. In the absence of data on the effect of intrinsic and extrinsic factors on the PK of VH3739937, and at the time of study initiation, the typical targeted doses were ~4x the minimal predicted efficacious dose.

Dose escalation in Part 2 (MAD) will be stopped in the event that safety or PK stopping criteria are not met, but if the Bayesian predicted probability is >50% that any participant's AUC(0-τ) on Day 14 in the subsequent Cohort 3 and 4, or on Day 18 in Cohort 5, or on or prior to Day 21 in Cohort 6 will exceed the MAD PK stopping criteria. In the event this occurs, the dose for the next cohort may be reduced such that the Bayesian predicted probability that any participant's AUC(0-τ) and the Cmax on Day 14 in the subsequent dose will exceed the MAD PK stopping criteria is ≤50%.

7.1.5. Clinical Criteria for Stopping the Study

Safety parameters and the available pharmacokinetic parameters from the previous cohorts will be fully assessed by the DEC before the next cohort is dosed. Any trends

towards drug-related changes 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.

If the following number of participants, within the ongoing cohort of 7 active participants, develops clinically significant changes in safety parameters not listed above or significant AEs thought to be drug related, the dose escalation will be paused until all of the cumulative safety data is reviewed by the DEC and the VSLC: The VSLC is comprised of senior representatives from various departments, including clinical development, toxicology, pharmacovigilance, epidemiology, and medical affairs. However, if any of the criteria are met, an optional cohort may be introduced to assess a lower tolerated dose.

- One participant experiences an AE of Grade 4 intensity or a Grade 4 clinically significant laboratory abnormality assessed as related to VH3739937, as reported by the PI.
- One participant experiences a Serious Adverse Event (SAE) or death assessed as related to VH3739937, as reported by the PI.
- If greater than 25% of participants within the same Period (SAD) or Cohort (MAD) receiving VH3739937 have a ≥ Grade 3 intensity AE or lab abnormality (with the exception of asymptomatic changes in lipid panel) or a ≥ Grade 2 intensity rash with concurrent fever, transaminase elevation or eosinophilia.
- 2 participants with confirmed QTcF ≥500 msec or a change from baseline of QTcF>60 msec, within the same Period (SAD) or Cohort (MAD)
- 2 participants with clinically significant, in the opinion of the PI, arrhythmias within the same Period (SAD) or Cohort (MAD)

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, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. Please see SRM for further detail.
- Please see SoA for data to be collected at the time of study discontinuation if occurs prior to discharge from unit, and if study discontinuation occurs post discharge from unit, and follow-up and for any further evaluations that need to be completed.
- 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

- Participants will be expected to be resident in the Phase I unit as per SoA. A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
  - The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or will 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 with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA
- Immediate safety concerns will be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study intervention.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA

8.1. Safety Assessments

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

8.1.1. 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 physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height and weight will be measured and recorded as indicated in the SoA
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.1.2. Vital Signs

- Single oral temperature, pulse rate, respiratory rate and blood pressure will be assessed.
- All blood pressure and pulse measurements will be assessed in semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). In addition, temperature will be monitored daily during study participation.
- Additional details can be found in the SRM.

8.1.3. Screening for COVID-19 Infection

- Study participants will be monitored at Screening and daily while inpatients for COVID-19 symptoms. Investigator(s) should utilise the World Health Organisation (WHO)_Case Definitions to classify COVID-19 cases [World Health Organisation, 2020]. While outpatients, participants should report to the unit any symptoms suggestive of COVID-19. All participants who experience symptoms suggestive of COVID-19 should be isolated in the unit or at home and tested for SARS-CoV-2 using an approved molecular test (PCR). The investigator should consider any participant testing positive for SARS-CoV-2 being discontinued from study drug if COVID-19 symptoms are moderate to severe. Appropriate contact tracing for all participants testing positive will be performed within the unit. This should be done in accordance with local

legislation and guidelines. Appropriate follow up should be implemented for participants who discontinue study due to COVID-19.

- Following Screening, all study participants will be admitted to the Phase I unit on Day -2 and tested for SARS-CoV-2.

- Participants in the Part 1 SAD treatment periods 2, 3 or 4 (if included) and in the RBA FE Cohort 7 will be tested for SARS-CoV-2 approximately one week prior to re-admission, at admission, and on re-admission to the unit as per the SoA. In addition all participants in Part 2 MAD Cohorts 3,4,5 and 6 will be tested for SARS-CoV-2 weekly while in the Phase I unit and at discharge.

- All study participants should be tested again for SARS-CoV-2 using an approved molecular test (PCR) prior to leaving the unit.

8.1.4. Electrocardiograms

- In Part 1, 12-Lead ECG will be performed on Day-1, Day 1 at pre-dose, and 1, 2, 4, 6, 12 and 16 hours post-dose. At all other timepoints, ECG will be performed at the pre-dose timepoint.
- In Part 2, 12-Lead ECG will be performed at the pre-dose timepoint at all timepoints indicated in SoA.
- In Part 3, 12-Lead ECG should be performed on Day 1 in Periods 1-3 at pre-dose, 2 h, and h post dose. Pre-dose ECGs in Periods 1-3 will be taken in triplicate.
- Triplicate 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 timepoints.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings will be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- If any abnormalities in ECG interval are noted (including prolongation of the QT interval), ECGs will be repeated in triplicate with recordings over a 5 minute time period. Refer to Section 7.1.2 for QTc Stopping Criteria and additional QTc readings that may be necessary.
- At least one of these ECGs will be available and reviewed by the PI on site to evaluate for QT prolongation to ensure subject safety. Additional safety ECGs beyond those described in the SoA may be printed at the discretion of the PI if prolongation in QT interval is suspected.
- Safety ECGs may be printed from the Global Instrumentation Holter device (see below). ECG parameters from safety ECGs will not be collected unless as part

of an observed adverse events. Refer to Section 7.1.2 for QTc Stopping Criteria and additional QTc readings that may be necessary.

- At timepoints for ECG extraction from Holter recordings, participants will be semi-supinely resting for at least 10 minutes.
- Once human data (eg Cmax) is known, the number of ECG time points may be reduced in subsequent dosing groups.
- Additional detail can be found in the SRM.

8.1.4.1. Cardiodynamic assessment (ECGs extracted from Holter recordings)

The frequency of ECG data in the SAD and MAD arises from emerging literature suggesting frequent QT evaluation early in development may mitigate the need for a formal TQT study [Darpo, 2014]. ECGs will be extracted as shown in the SoA from the SAD and the MAD component of the study. Should clinical development of VH3739937 continue, an exploratory objective of this study is to assess the exposure-response relationship between VH3739937 and QTcF following single and repeat dose administration.

The 12-lead Holter and ECG equipment will be used and may be supplied and supported by eREsearchTechnology, Inc. (ERT) or the contract research organization (CRO). All ECG data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12 lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. ECGs to be used in the analyses will be selected by pre-determined time points as defined in the SoA, and will be read centrally by ERT, Inc.

The following principals will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit and treatment allocation
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods utilized by ERT's core laboratory.

TQT Plus ECG Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT, Inc. The method enables extraction of ECGs with the lowest heart rate (HR) variability and noise within the protocol-specified extraction time window (e.g., the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

High-Precision QT Analysis

High-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc or RR from beat to beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" is performed using COMPAS software. All low confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR value from each extracted replicate is calculated, and then the mean of all available medians from a nominal timepoint is used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

Table 12 T-wave morphology categories (assessed manually)

Category	Description
Normal T-wave	Any T-wave not meeting any criterion below
Flat T-waves	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave

In addition to the T-wave categorical analysis, the presence of abnormal U-waves is noted.

8.1.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention will be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol- required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA

8.1.6. Suicidal Ideation and Behaviour Risk Monitoring

VH3739937 is not thought to penetrate the CNS and is not being developed for a neurologic or psychiatric condition. Based upon the clinical data from the VH3532795 clinical program, where two healthy volunteers reported CNS SAEs at supratherapeutic doses, participants will be excluded based on any pre-existing psychiatric condition (including assessment using the CSSRS).

In addition, participants in the study will have assessment by the CSSRS during the on-treatment phase of the study (see SoA for details). As described in Section 7.1, any positive (abnormal) response confirmed by the investigator during the on-treatment phase will result in their discontinuation. In either case (screening or on-treatment) of positive (abnormal) response confirmed by the investigator, the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. Please see the SRM for further details.

8.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

As described in Appendix 3 and Appendix 6, intensity of AEs (and lab abnormalities) will be graded using the division of AIDS (DAIDS) Grading table. While the study population will consist of HIV-1 seronegative healthy volunteers, the DAIDS criteria will be used in later clinical trials (Phase 2a and beyond). Additionally, the DAIDS criteria have a more conservative grading scale relative to others. Thus, participant safety evaluation and monitoring will be more conservative.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for

following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention and/or study (see Section 7).

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

- All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the time points specified in the SoA However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. For further detail, please see Appendix 3
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.2.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3.). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 5 days [at least 5 terminal half-lives] after last dose of study intervention.
- If a pregnancy is reported, the investigator will inform GSK within 24 hours of learning of the pregnancy and will follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3. Treatment of Overdose

For this study, any dose of VH3739937 greater than a planned dose level within a 20-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose, the Investigator should:

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

3. Obtain a plasma sample for PK analysis within 24 hours from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant. No dose modifications are permitted without prior discussion and consent from the DEC.

8.4. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of VH3739937 at timepoints specified in the SoA. Details of blood collection and processing of PK samples are detailed in the SRM.
- Whole blood samples of additional approximately 2 mL will be collected in SAD cohort 1 only for acidification purpose. Concentrations from acidified samples will be compared to concentrations from non-acidified samples and will be reported as exploratory data.
- The number of PK sampling time points may be reduced in the initial MAD cohort as well as further in subsequent MAD dosing groups once human PK data are available in the SAD as well as in the initial MAD cohorts.
- An additional 2 mL of whole blood samples will be collected for metabolite profiling of VH3739937 at the same timepoints as the PK samples on Day 1, Day 2, Day 14, Day 15 in MAD cohorts 3, 4 and 5, and on Day 18, and Day 19 in the MAD cohort 5 only, as specified in the SoA. The results will be reported under a separate protocol. Details of blood collection and processing are detailed in the SRM.
- A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection, processing, handling and shipping procedures of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- In Part 1, Cohort 2 Period 3 only, pre-dose urine can be collected up to 3.5 h pre-dose for analysis of VH3739937 renal excretion. Afterward urine will be collected for analysis of VH3739937 renal excretion over 24 h collection periods as follows: 0-24 h, 24-48 h, 48-72 h, 72-96 h. Fresh spot urine collection will be taken at each outpatient visit. For further detail, please see SRM.
- In Part 2, urine PK and metabolite samples for analysis of VH3739937 will be collected at pre-dose (20 mL) (within 1 h prior to dosing) and from time 0 up to24 h post dosing on Day 1 and from time 0 to 24 h post dosing on Day 14 in MAD Cohorts 3 and 4. Spot urine sample collection on Day 16, 17 18, and 19 at post dose timepoint used on Day 1. Fresh spot urine collection will be taken at each outpatient visit for urine PK sampling for analysis of VH3739937.

- In Part 2, Cohort 5, urine PK and metabolite samples for analysis of VH3739937 will be collected at pre-dose (40 mL) (within 1 h prior to dosing) and from time 0 up to 24 h post dosing on Days 1, 14 and 18. Spot urine sample collection on Day 20, 21, 22, and 23 at the post dose timepoint on Day 1. Fresh spot urine collection will be taken at each outpatient visit for urine PK sampling for analysis of VH3739937.
- In Part 2, Cohort 6, urine PK samples for analysis of VH3739937 will be collected at pre-dose (20 mL) (within 1 h prior to dosing) and from time 0 up to 24 h post dosing on Days 1, 8 and 15. Fresh spot urine collection will be taken at each outpatient visit for urine PK sampling for analysis of VH3739937.
- After PK analysis, aliquots of 200 mL pooled urine samples (0-24 h) will be used for metabolite profiling. A maximum of 2 urine samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The actual start and stop date and time (24-h clock time) as well as collected volume over 24 h will be recorded for urine sample. Details of PK urine sample collection, processing and handling, storage procedures and shipping procedures are detailed in the SRM
- Duodenal bile samples will be collected on Day 18 only for the analysis of VH3739937 and its metabolites for participants in MAD Cohort 5 only.
- The EnteroTest or EnteroTracker will be swallowed 2 h post-dose. After approximately 6.5 h the bile string will be removed. Bile fluid is recovered on a highly absorbent nylon line which is contained within a weighted gelatin capsule. The 140 cm EnteroTest line or 90 cm EnteroTracker 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 EnteroTest/EnteroTracker sample collection, processing, storage and shipping procedures are provided in the SRM.
- The metabolite profiling of the plasma, bile and urine samples will be conducted under separate protocols and the results are reported separately according to the protocols.
- Residual plasma and urine samples from all cohorts after PK bioanalysis may be used for metabolite identification and profiling purpose.
- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.
- For Part 3, samples collected for VH3739937 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study. Once the plasma has been analysed for VH3739937, any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate protocol.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A genetic sample is not required in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal statistical hypotheses are to be tested.

9.2. Sample Size Determination

9.2.1 Sample Size Assumptions

Parts 1 and 2
Sample size is based on feasibility. No formal calculation of power or sample size (i.e., sample size sensitivity or robustness) for Parts 1 and 2 of the study has been performed. A sample size of approximately 9 participants (6 active: 3 placebo) per dose-cohort should be sufficient to provide useful estimates of both inter- and intra-participant variability for VH3739937, PK parameters, and initial safety assessment.

Sample size re-estimation is not planned.

Data will be reviewed by the DEC prior to each dose escalation; no other interim analysis is planned.

Part 3
This is the first study which will evaluate the pharmacokinetic properties of VH3739937 in humans following oral administration of suspension and tablet formulations. Results from previous PK studies for GSK3640254 (a similar compound to VH3739937), and observed preliminary data from Part 1 of the study suggest that 25% is a conservative estimate for percent within subject coefficient of variation (%CVw) of Cmax and AUC(0-t) and will therefore be used to assess the precision (i.e. half width of the 90% confidence interval on the log and ratio scale) potential sample sizes of this three period crossover RBA/FE study. Assuming a within participant coefficient of variation of 25% and a sample size of 12 participants, it is estimated that the half width of the 90% confidence interval for the formulation difference on the log-scale will be within 0.173 of the point estimate (assumed to be 1.0). If the point estimate of the ratio of geometric means is assumed to be 1.0, then the 90% confidence interval will be approximately (0.841, 1.189) on the original scale.

Since tablet formulation and amount of food consumed may change the exposure to VH3739937, a range of point estimates for true ratio of 0.9, 1.0, and 1.1 were used in combination with sample sizes ranging from 12 to 18. The resulting estimated 90% confidence intervals are shown in Table 13 below.

Table 13 90% Confidence Intervals for RBA/FE of VH3739937

n	%CVw	Point Estimate	90% CI
12	25	0.9	(0.757, 1.070)
12	25	1	(0.841, 1.189)
12	25	1.1	(0.925, 1.308)
15	25	0.9	(0.772, 1.049)
15	25	1	(0.858, 1.166)
15	25	1.1	(0.944, 1.282)
18	25	0.9	(0.783, 1.034)
18	25	1	(0.870, 1.149)
18	25	1.1	(0.957, 1.264)

9.2.2 Sample Size Sensitivity

To assess the sensitivity of sample size to within participant variability of the PK parameters, point estimates and 90% confidence intervals for a sample size of 12 participants with a true ratio of 1.0 were calculated for %CVw values ranging from 15% to 35% were also considered and shown in Table 14 below.

Table 14 Sample Size Sensitivity for RBA/FE of VH3739937

N	%CVw	Point Estimate	90% CI
12	15	0.9	(0.810, 1.000)
12	25	0.9	(0.757, 1.070)
12	35	0.9	(0.708, 1.143)
12	15	1	(0.900, 1.111)

N	%CVw	Point Estimate	90% CI
12	25	1	(0.841, 1.189)
12	35	1	(0.787, 1.270)

Approximately 18 participants will be enrolled to ensure that approximately 12 evaluable participants complete the study.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All participants who received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they received.
Pharmacokinetic Concentration	The PK Concentration Population will include all participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the concentration listing.
Pharmacokinetic Parameter	The PK Parameter Population will include all participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listing, plotting of the concentration-time data and PK parameter summary.

9.4. Statistical Analyses

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population and details will be provided in the Reporting and Analysis Plan (RAP).

Endpoint	Statistical Analysis Methods
Primary	Safety data will be presented in tabular and or graphic format and summarized descriptively accordingly to GSK's Integrated Data Standards Library (IDSL) standards
Exploratory	Will be described in the reporting and analysis plan

AEs will be tabulated using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentage of participants experiencing each specific AEs (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. 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. AEs leading to withdrawal will also be summarized by treatment.

9.4.2. Other Analyses

PK and pharmacodynamic exploratory analyses will be described in the reporting and analysis plan. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

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

9.4.3. Pharmacokinetic Analyses

Plasma VH3739937 concentration-time data will be analyzed by noncompartmental methods using WinNonlin Professional 5.2 or higher, Phoenix (Pharsight Corporation) or comparable software. The various analyses will be conducted as permitted by data available. Individual plasma PK parameters for each participant and dosing group will be determined, including:

- Part 1 (single dose): $AUC_{(0-24)}$, $AUC_{(0-\tau)}$, $AUC_{(0-inf)}$, Cmax, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F.
- Part 2 (repeated once daily [QD] dose):
  - Day 1: $AUC_{(0-24)}$, C_{max}, C_{24}, t_{max}, t_{lag}
  - Day 14 (Cohort 3 and 4): $AUC_{(0-\tau)}$, C_{max}, $C\tau$, t_{max}, $t_{1/2}$, and CL/F
  - Day 18 (Cohort 5): $AUC_{(0-t)}$, C_{max}, Ct, t_{max}, $t_{1/2}$, and CL/F
- Part 2 (repeated once weekly [QW] dose):
  - Day 1 (Cohort 6): $AUC_{(0-168)}$, C_{max}, C_{168}, t_{max}, t_{lag}
  - Day 15 (Cohort 6): $AUC_{(0-t)}$, C_{max}, Ct, t_{max}, $t_{1/2}$, and CL/F
- Part 3 (Single Dose Relative Bioavailability):
  - $AUC_{(0-24)}$, $AUC_{(0-inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F

9.4.4. Statistical Analysis of Pharmacokinetic Data

- Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK.
- Plasma VH3739937 concentrations and PK data will be summarized by treatment and listed by participant. Unless stated otherwise, descriptive summaries will include number (n), mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum for continuous variables, n and percent (%) for categorical variables, and geometric mean, 95% confidence interval (CI), and the between-participant CV (%CVb) for the log-transformed PK parameters.
- Dose proportionality of selected single and repeated dose PK parameters will be assessed by the power model.

- Accumulation will also be:
    - Predicting from single dose data (Part 1) based on AUC as follows: Rp = AUC(0-∞) day 1/ AUC(0-τ) day 1
    - Evaluated for each treatment by determining the ratio of Day 14 for cohort 3 and 4, Day 18 for cohort 5, and Day 15 for cohort 6 (Part 2) to Day 1 AUC(0-τ) (R(AUC(0-τ)), Cmax (R(Cmax)), and Cτ (R(Cτ)). C24 on Day 1 will be taken as the Cτ on that day.
- Assessment of steady-state VH3739937 concentrations will be assessed in Part 2 by estimating the slope of pre-dose concentrations on Days 2-14 for Cohorts 3 and 4, Days 2-18 for Cohort 5 and Days 2-15 for Cohort 6. The final assessment of the slope will be determined by at least the last 3 pre-dose concentrations.
- **Part 3**
  For the assessment of relative bioavailability of formulation and food effect (if conducted), the $\log_e$-transformed PK parameters will be analysed as data permits using separate mixed effect models with a fixed effect term for fed vs. fasted and tablet vs PiB. Participant will be treated as a random effect in each model. Point estimates and their associated 90% CIs will be calculated for the difference in $AUC_{(0-24)}$, $AUC_{(0-inf),}$ and C_{max} for the tablet vs PiB and fed vs fasted comparisons. The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of tablet vs PiB and fed vs fasted in PK parameter values on the original scale.
- Full details of the statistical analysis of PK data will be described in the RAP.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

- Pharmacokinetics/Pharmacodynamic (PK/PD) analyses will be performed only if the VH3739937 development project is progressing forward. The end point for the potential impact of VH3739937 on cardiac repolarization will be the change-from-baseline QTcF (ΔQTc). A modelling approach will be used to describe the relationship between VH3739937 concentration and QTc data.
- The details of the PK/PD analysis will be described in the RAP or in a separate analysis plan if the analysis is reported separately.

9.5. Interim Analyses

There will be no formal interim analysis; however, all preliminary safety, tolerability, and available pharmacokinetic data will be reviewed internally at the Dose Escalation Committee (ViiV/GSK) prior to each dose escalation or administration and according to the dose escalation charter. Safety data (labs, vital signs, ECG, AEs, SAEs) will be reviewed by the PI/Sub-I and ViiV/GSK study team after completion of each dose level. Dose escalation can only occur after PI/Sub-I and ViiV/GSK study team has found that the safety, PK profiles are supportive to proceed with the evaluation of the next highest dose level.

At each dose, the Bayesian probability of an individual exceeding the Cmax threshold in Part 1 and the Bayesian probability of an individual exceeding the AUC threshold in Part 2 will be calculated and compared with 50%. This will be used to help selection of the next dose together with safety and tolerability data. The Bayesian probability will be based on Whitehead's model shown below [Whitehead, 2001] using non-informative prior for model parameters.

$$y_{ij} = \theta_1 + \theta_2 d_{ij} + s_i + \epsilon_{ij} \quad [1]$$

Where y_{ij} is log-PK of i-th participant to j-th dose, d_{ij} is j-th log-dose administered to i-th participant. θ_1 and θ_2 are population intercept and slope, respectively. s_i is random effect of i -th participant and ϵ_{ij} is random error of i -th participant in j-th dose.

When intra-participant variability cannot be estimated during PK predictions in Part 1 (i.e., early on in the study when there is not sufficient information to estimate intra-participant variability) and for conducting prediction of all doses in Part 2, the same Whitehead's model will be used for Bayesian probability calculations as below.

$$y_i = \theta_1 + \theta_2 d_i + \epsilon_i \quad [2]$$

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

Bayesian model Operating Characteristics (OC)

In this part, we want to explore the operating characteristics of the possibility of escalating to the 800 mg dose in the SAD portion of the study. Given different assumptions of with-in and between participant Cmax variability (CV%), and assuming dose proportionality (slope=1), data for 1000 trials were simulated based on Whitehead's model [1]. Each simulated trial contains Cmax values for 6 subjects on treatment for doses ranging from 10 mg to 640 mg in SAD cohort 1 and cohort 2.

For each simulated trial, we fit the mixed effect Bayesian model based on mode [1]. Using the following procedure, we calculated the Bayesian probability of an individual exceeding the Cmax threshold:

10,000 iterations were simulated in the MCMC procedure. In each iteration, we obtained the estimated parameters $\hat{\theta}_1, \hat{\theta}_2, \hat{s}_i$ $(i = 1,2, \dots, 6)$ and $\hat{\sigma}^2$(the estimated standard deviation of ϵ_{ij}), Based on the estimation, a random sample for each subject, which represented the simulated exposure in the 800 mg dose, was drawn from the distribution $N\left(\hat{\theta}_1 + \hat{\theta}_2 \times 800 + s_i, \hat{\sigma}^2\right)$. We counted the number of iterations N with any simulated exposure exceeding the Cmax threshold log(21). The Bayesian probability was calculated as $1 - \frac{N}{10{,}000}$. .

For each trial, the Bayesian probability of the 800 mg dose exceeding the Cmax threshold of log(21) was calculated and compared with different thresholds (40%, 50% or 60%). Results showed that all simulated trials had a probability less than 40%, 50%, and 60% in situations with high variability (%CVw = 50, %CVb = 50) as well as scenarios with low variability (%CVw = 12.5, %CVb = 25). These results indicate that the probability of escalating to 800 mg in the SAD is high.

Additional simulations were conducted to determine the probability of escalating to 100 mg during the Part 2 of the study (MAD QD dosing). 1000 simulated trials were produced for each value of %CVb (25, 35, and 50), using a predicted 24-hour steady state AUC of 39.8 µg*h/mL. More detailed information may be found in the IB Supplement [GlaxoSmithKline Document Number 2021 RPS_CLIN_004025]. For each trial, the Bayesian probability of the 100 mg MAD QD dose producing an 24 hour steady state AUC above log(96.2) was calculated. This value was compared to potential evidence thresholds of 40%, 50%, and 60%. Table 15 shows the probability of a simulated trial having a Bayesian predictive probability of exceeding the AUC safety threshold of log(96.2) less than the various threshold values under the chosen values of CVb.

Table 15 Percentage of simulated trials of 100 QD dosing with Bayesian predicted probability of 24hr steady state AUC under safety threshold of log(96.2) across probability thresholds

AUC Variability	Probability Threshold		
%CVb	40%	50%	60%
25	0.995	0.999	1
35	0.934	0.967	0.986
50	0.791	0.880	0.927

These results indicate that the probability of escalating to 100 mg during the MAD QD dosing portion of the study is high.

Finally, simulations were performed to assess the probability of any participant having an 24 hour steady state AUC above log(96.2) or a Cmax above log(21) during the weekly MAD dosing portion of the study. It is anticipated that a 500 mg weekly dose will produce a steady state maximum daily AUC of 31.2 µg*h/mL. Under this assumption, 1000 simulated trials were produced for each value of %CVb (25, 35, 5). Each simulated trial included 7 participants dosed at 500 mg. No simulated trial produced any participant who had either an AUC above log(96.2) or a Cmax above log (21). Therefore, the probability of a subject exceeding the safety threshold during the weekly dosing portion of the study is low.

9.6. Final Analyses

Final analysis 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 for each part.

Unless stated otherwise, descriptive summaries will include n, mean, SD, %CV, median, minimum, and maximum, geometric mean with associated 95% CI, and the %CVb for continuous variables, whereas n and percent will be used as summary statistics for categorical variables.

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, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

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.
- 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

This study will be reviewed and approved by an Internal Review Committee prior to initiation.

10.1.6. 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.

10.1.7. 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 GSK site or other mutually-agreeable location.
- ViiV/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- ViiV/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 GSK Policy.
- ViiV/GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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 (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 and/or Task Order between ViiV/GSK and the study site.

- 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.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 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.
- 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 the study and deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the 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.
- The clinical site in this study, utilizes a validated proprietary bedside data capture system to retain the source data.

10.1.10. Study and Site Closure

ViiV/GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 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.
- Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) will be conducted at monthly intervals during intervention and at the end of relevant systemic exposure.
- 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.

Table 16 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium, Chloride, Bicarb	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium, Magnesium, Phosphate	Alkaline phosphatase	Amylase
	Lipase	Fasting Lipid Panel (Cholesterol, Triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL])	Serum creatine phosphokinase (CPK)	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick			

Laboratory Assessments	Parameters
	• Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed) • Fourth generation serology test for HIV-1, hepatitis B surface antigen [HbsAg], and hepatitis C virus antibody)] • The results of each test must be entered into the CRF.

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 Appendix 5 All events of ALT ≥3 × upper limit of normal (ULN) and 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 as an SAE (excluding studies of hepatic impairment or cirrhosis).

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **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.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (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.

Results in persistent 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that

may not be immediately life-threatening or result in death or hospitalization but 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug 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 (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by 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 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

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to ViiV/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ViiV/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.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV/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 ViiV/GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to ViiV/GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to ViiV/GSK

SAE Reporting to ViiV/GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to ViiV/GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - 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), 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.
3. 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/mL is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Highly Effective Methods of Contraception

• **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
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. 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, 121ymptom-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for the study. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive VH3739937
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- 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.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will discontinue study intervention and be withdrawn from the study.

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

Table 17 Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT≥3xULN If ALT≥3xULN **AND bilirubin**[1,2] ≥ 2xULN (>35% direct bilirubin) or **INR** >1.5, Report as an SAE. See additional Actions and Follow Up Assessments listed below

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5** • Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hours** • Monitor participant(s) twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended	• Viral hepatitis serology[3] • Obtain international normalized ratio (INR) and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic analysis, obtained as soon as possible in relation to last dose[4] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • 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 AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form

Liver Chemistry Stopping Criteria	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant(s) weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) 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 (gM) antibody; HbsAg and HbcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM. .

10.6. Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. For more information, please refer to the DAIDS grading table Version 2.1, July 2017 at (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).

10.7. Appendix 7: Permissible Procedures During COVID-19 Pandemic

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participants ability to attend clinic visits. Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to allow flexibility to facilitate conduct of the study.

Permissible changes to procedures during the COVID-19 pandemic if deemed necessary by the investigator are outlined below. The investigator should discuss with the medical monitor the rationale prior to these changes being implemented for a participant(s). Any change implemented will be documented in each participant's medical notes and in the eCRF as a COVID-19 related protocol deviation.

1) Participants previously deemed eligible during the screening period unable to attend within the allowable screening window due to COVID-19 may be rescreened. The most recent screening data will be used to determine study eligibility.
2) Duration of admission to the clinic may be extended if deemed necessary by the investigator due to the COVID-19 pandemic.
3) Duration of study participation may be extended as a result of a pandemic restrictions. Parexel staff shall continue to monitor participant status via phone call until participant is able to return and complete protocol required study procedures.
4) Participants are required to have two negative SARs-CoV-2 PCR tests prior to/on each (re-)admission to the unit. Participants will also undergo weekly testing while on the unit and on discharge as appropriate. Additional testing for SARS-CoV-2 may be introduced to the SoA at different times if deemed necessary by the investigator and/or sponsor.

If a participant has suspected COVID-19, or tests positive for COVID-19, or has potential COVID19 exposure while enrolled in the study, the Investigator must assess the impact of this disease/situation on the benefit/risk for the participant/(s) to continue in the study, as well as compliance with protocol withdrawal criteria. Adverse events related to COVID-19 should continue to be evaluated as to whether they meet SAE criteria as defined in Section 10.3.2, and if so, reported in line with the SAE reporting requirements (Section 10.3.4). Investigator(s) should utilise the WHO Case Definitions to classify COVID-19 cases [World Health Organisation 2020]. The Sponsor recognises that COVID-19 case definitions may evolve during the study period, the most recent edition should be consulted for each case. For all AEs or SAEs related to COVID-19, details should also be entered into the specific COVID-19 eCRF. The study site should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation in the setting of clinically defined mild COVID-19 infection.

All cases of COVID-19 must be properly documented in the participant's medical chart. Any participant withdrawing due to COVID-19 disease symptoms/diagnosis may be replaced following discussion between the Investigator and Sponsor.

10.8. Appendix 8: Abbreviations and Trademarks

µg	Micrograms
ΔQTcF	Change-from-baseline QTcF
%CV	Coefficient of variation
%CVw	Within-participant coefficient of variation
%CVb	Between-participant coefficient of variation
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ARV	Anti-retroviral
ART	Anti-retroviral therapy
ALT	Alanine transaminase
AST	Aspartate Aminotransferase
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
AUC(0-24)	Area under the plasma concentration time curve from zero to 24
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the plasma concentration time curve from zero (pre-dose) to t
BID	Twice daily
BMI	Body mass index
BMS	Bristol-Myers Squibb
bps	Beats per minute
BUN	Blood urea nitrogen
Cτ	Trough serum concentration
C24	Drug concentration at 24 hours post-dose
cART	Combination anti-retroviral therapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIB	Clinical Investigator's Brochure

CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent oral clearance
Clast	Last observable concentration
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Disease caused by corona virus SARS-CoV-2 first observed in 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CSSRS	Columbia Suicide Severity Rating Scale
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CYP	Cytochrome P450
DAIDS	Division of AIDS
DEC	Dose Escalation Committee
dL	Decilitre
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency
ERT	eResearch Technology, Inc
FDA	Food and Drug Administration
FE	Food Effect
FSH	Follicle stimulating hormone
FTIH	First-time-in-human
g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal

GLP	Good laboratory practice
GSK	GlaxoSmithKline
h	Hours
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HDL	High-density lipoprotein
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human immunodeficiency virus-1
HPMC	Hydroxypropyl methyl cellulose
HR	Heart Rate
HRT	Hormone Replacement Therapy
HSR	Hypersensitivity reactions
IC50	Half maximal inhibitory concentration
ICF	Informed consent form
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IIV	Inter-Individual Variability
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	Kilograms
L	Litres
LA	Long Acting
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase

LDL	Low-density lipoprotein
LOAEL	Lowest observed adverse effect level
m^2	Meter square
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Maturation inhibitors
mins	Minutes
mIU	milli-international units
mL	Milliliter
MOA	Mechanisms of action
MRSD	Maximum Recommended Starting Dose
MSDS	Material Safety Data Sheet
msec	Milliseconds
ng	Nanograms
NOAEL	No observed adverse effect level
OC	Operating Characteristics
PBA	Protein Binding Adjusted
PBO	Placebo
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PI	Principal Investigator
PiB	Powder-in-bottle
PK	Pharmacokinetic
PLHIV	People living with HIV
POC	Proof of Concept
QD	Once Daily
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	Quality tolerance limit

QW	Weekly Dosing
RAP	Reporting and Analysis Plan
RAMOS NG	Randomization and Medication Ordering System Next Generation
RBA	Relative Bioavailability
RBC	Red blood cell
R ($C\tau$)	Ratio of concentration over the dosing interval
RAUC(0-τ)	Accumulation ratio of area under the concentration-time curve over the dosing interval
R(C_{max})	Ratio of maximum observed concentration
Rp	Predicted accumulation ratio
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious Adverse Event
SARS-CoV-2	SARS Coronavirus-2
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Oxaloacetic Transaminase
SI	Sub-investigator
SOA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
tlast	Time of last observable concentration
tlag	Lag time
Tmax	Time of occurrence of Cmax
TOC	Table of Contents
ULN	Upper limit of normal
VH	ViiV Healthcare
WBC	White blood cells
WHO	World Health Organisation

WOCBP	Women of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
DAIDS
Phoenix
WinNonlin

10.9. 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).

Amendment [01] 11-JUN-2020

Overall Rationale for the Amendment: Amendment 01 was generated to remove Sodium Stearyl Fumarate from the placebo formulation, to clarify administration for study interventions and maintenance of the blind. Revisions were made to the study eligibility criteria and safety assessments in response to the FDA's feedback and to mitigate the potential risks for study conduct during the COVID-19 pandemic. Given the absence of benefit to study participants, the exclusion criteria and the criteria for individual subject discontinuation, dose escalation and stopping the study were revised to be more conservative. Revisions were made to improve accuracy of the study risk assessment and the pharmacokinetic analyses.

Section # and Name	Description of Change	Brief Rationale
Title page	Included the EudraCT number for this study	The EudraCT number had been obtained
1.2 Schedule of Activities (SOA)	SOA for the SAD and MAD revised to include monitoring of temperature on each day of study participation and SARS CoV-2 testing at Screening, on admission to the Phase I unit and on day of discharge from the unit. Revision to clarify that ECG and vital signs are collected pre-dose and that bile sampling will be performed post-dose	To mitigate risk to study conduct during the COVID-19 pandemic and to clarify scheduled activities
2.3.1 Risk Assessment	Included updated information for gastrointestinal events and included Skin and Subcutaneous Tissue Disorders as a new risk category	Inclusions to ensure accuracy of this section
2.3.4 Acute Monitoring in FTIH Studies	Revised to state this study may be conducted in more than one Phase I Unit	Improve clarity of information in this section
5.1 Inclusion Criteria	Included a new criterion for participants to have two consecutive negative tests for SARS CoV-2 at Screening and on admission	To mitigate risk to study conduct during the COVID-19 pandemic
5.2 Exclusion Criteria	Included two new criteria excluding participants having signs and symptoms suggestive of COVID-19 and participants who had contact with a known COVID-19 positive person/s within 14 days prior to admission Included new criterion and revised existing criterion	To mitigate risk to study conduct during the COVID-19 pandemic. Exclusionary laboratory criteria expanded and made more conservative to facilitate improved assessment of a potential safety signal

Section # and Name	Description of Change	Brief Rationale
	addressing laboratory parameters for haemoglobin, liver and renal function. Extended exclusion criterion addressing prior and concomitant therapy to include cytochrome p450 enzyme inducers or inhibitors.	
6.1 Study Intervention(s) Administered	Revision to details of Study Interventions	Removal of Sodium Stearyl Fumarate from the placebo
6.2 Preparation/Handling/Storage /Accountability	Revision to clarify maintenance of the blind	The revised placebo formulations may be distinguished visually from the active GSK3739937 formulation
6.3 Method of Treatment Assignment	Revised to improve clarity on use of RAMOS NG for study randomisation and on emergency unblinding procedures	Implementation of use of RAMOS NG for randomisation of participants
6.4 Measures to Minimize bias: Randomization and Blinding	Revision to the method of administration of study interventions. Included additional information regarding unblinding in an emergency situation.	To minimise unblinding due to visual differences between the active GSK3739937 and placebo formulations. Extended information provided to address unblinding.
6.6 Concomitant Therapy	Revised to include cytochrome P450 (CYP) inducers and inhibitors as prohibited medications	Possible interaction of GSK3739937 with CYP inhibitors and inducers has not yet been excluded
6.7 Dose Modification	Revised to clarify that criteria for discontinuation of dose escalation also apply to discontinuation of dosing within the cohort in which a toxicity occurs	Revision to include additional detail regarding dosing and dose escalation
7.1 Discontinuation of Study Intervention	Included an additional criterion for discontinuation of the study intervention and	Inclusion of more conservative criteria for discontinuation of the study intervention and for

Section # and Name	Description of Change	Brief Rationale
	in 7.1.5 'Clinical criteria for stopping the Study' extended the criteria cited that would lead to pausing or stopping the study	pausing or stopping the study
8.1 Safety Assessments	8.1.1. 'Physical Examination' revised for clarity. 8.1.2 'Vital Signs' was revised to include temperature monitoring daily for study participants. A new sub-Section 8.1.3 'Screening for COVID-19' was included 8.1.4 'Electrocardiograms' revised to state a semi-supine position for Holter recordings	To mitigate risk to study conduct during the COVID-19 pandemic and revision of 8.1.1 and 8.1.4. to assist clarity and study conduct
9.4.3 Pharmacokinetic Analysis	Revised to correct pharmacokinetic analyses in Part 2.	Revision made to be consistent with study objectives
9.4.4 Statistical Analysis of Pharmacokinetic Data	Revised to be consistent with the revision to pharmacokinetic analyses in Section 9.4.3	Revised for accuracy and to be consistent with Section 9.4.3
10.2 Appendix 2: Clinical Laboratory Tests	Revised to remove urine test for pregnancy and to include the 4th generation serologic test for HIV-1	Revised for accuracy and clarity
10.7 Appendix 7: Permissable Procedures During COVID-19 Pandemic	Revised to clarify evaluation and reporting of adverse events and serious adverse events related to COVID-19 and reference to the World Health Organisation case definitions for COVID-19	Improve clarity on the procedures and guidance provided
10.8 Appendix 8: Abbreviations and Trademarks	Revised to include the abbreviations included in revisions in this protocol amendment	Inclusion of all abbreviations cited

11. REFERENCES

Darpo B., Garnett C., Benson C.T., Keirns J., Leishman D., et. al. Cardiac safety research consortium: Can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward. Am Heart J 2014; 168:262-72.

Fact sheet: United Nations AIDS. Global HIV & AIDS statistics. 2019 fact sheet; Available at http://www.unaids.org/en/resources/fact-sheet. Accessed 16-APR-2020

GlaxoSmithKline Document Number 2016N297636_00. Clinical Study Report AI468049 (206221). Completion Date: 15 August 2016.

GlaxoSmithKline Document Number 2016N302783_00. Clinical Study Report AI468038 (205891). Completion Date: 26 May 2016.

GlaxoSmithKline Document Number 2017N319618_00. Clinical Study Report AI468063 (206294). Completion Date: 23-December 2015.

GlaxoSmithKline Document Number 2017N332341_00. Clinical Study Report AI468044 (206220). Completion Date: 14-October 2016.

GlaxoSmithKline Document Number 2018N392814_01. Clinical Study Report (207187). Completion Date: 9-September 2018.

GlaxoSmithKline Document Number 2019N421306_00. GSK3739937 Investigator's Brochure_2019_Version00_GSK3739937. Effective Date: March 2020.

GlaxoSmithKline Document Number 2020N427033_00. Modeling and Simulation Analysis Report to predict the Pharmacokinetics and Pharmacodynamics of GSK3739937 for FTIH Study. Effective Date: 05-March-2020.

GlaxoSmithKline Document Number RPS_CLIN_004025. GSK3739937 Investigator's Brochure Supplement 02_2021_Version00_GSK3739937. Effective Date: March 2021.

Guidance for Industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. FDA/CDER., July 2005.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007; 164:1035-1043.

Whitehead J. et al., Easy-to-implement Bayesian methods for dose-escalation studies in healthy participants, Biostatistics, 2, 47cs, 2, 47v 2001.

World Health Organisation March 2020: Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim

guidance.https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov) Link accessed on 3rd June 2020