TITLE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of GSK3732394 in Healthy Participants

Protocol Number: 207863

Short Title: GSK3732394 First-Time-in-Human Study

Compound Number: GSK3732394

Sponsor Name and Legal Registered Address:

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UK

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. 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 131394

Approval Date: 12-SEP-2019

SPONSOR SIGNATORY

PPD

Max tailiade, DO
Vice President, Clinical Development,
ViiV Chief Scientific and Medical Office

SEP-12-2019
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 03, DNG 2017N341355_03	12-SEP-2019
Amendment 02, DNG 2017N341355_02	02-JUL-2019
Amendment 01, DNG 2017N341355_01	06-JUN-2019
Original Protocol, DNG 2017N341355_00	11-APR-2019

Amendment 03, 12-SEP-2019

Overall Rationale for the Amendment: This amendment is based on 3 criteria.

1) Initial dose escalation data following completion of Cohort 1 indicated that Cohort 6 in the study design will be required. Flexible language to this affect has been removed.
2) Initial dose escalation data following completion of Cohort 1 indicate that anti-drug antibodies (ADA) have the potential to appear earlier than indicated pre-clinically. Day 7 and Day 10 collection of samples for ADAs have been added in Part 1 and for Day 8 in Part 2.
3) The previous consensus between the Sponsor and the Study Site on CD4+ T-cell count and CD4 percent values screening values under Amendment 02, requires further clarification.

Section # and Name	Description of Change	Brief Rationale
Synopsis Schematic, Section 5.1 – Overall Design, Paragraph 1 and Part 1, Paragraph 2	Revised to reflect that Cohort 6 is now a part of the study design and is not optional. Participant numbers are updated to reflect Cohort 6 inclusion (Part 1 n = 48 from n = 40).	See item 1 above.
Section 2 – Schedule of Activities, Table 2 and Table 4	Day 7 and Day 10 collection of samples for ADAs have been added in Part 1 and for Day 8 in Part 2.	See item 2 above.
Section 6.2 – Exclusion Criteria, Criterion 24 and Section 3.3.1-Risk Assessment Table -2nd bullet for CD4+ cell reduction / Impairment in Immune Function	Absolute CD4+ T-cell count **<500 cells** or CD4 percent (CD4%) outside of the normal range for the reference laboratory (**32% to 64%).**	See item 3 above.
Section 8.1.1.1 – Serious Allergic Reaction, 2nd bullet	A delayed hypersensitivity reaction AE **with systemic symptoms and/or end-organ effects** (i.e., serum sickness, vasculitis, fever, arthralgia/myalgia, nephritis, etc.) of moderate to severe intensity (Grade 2-4 by DAIDS criteria)	Bolded language added to provide clarity
Not applicable	Other administrative changes for items such as typographical errors or grammatical corrections.	Clarity

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1. SYNOPSIS

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of GSK3732394 in Healthy Participants

Short Title: GSK3732394 First Time in Human Study

Rationale:

With the introduction of effective combination therapies, Acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality has declined significantly and, in many parts of the world, human immunodeficiency virus (HIV)-infection has been transformed into a treatable chronic condition. Despite the availability of a number of potent and safe antiretroviral agents (ARVs) across different therapeutic classes and the availability of one pill per day regimens, the burden of lifetime daily dosing remains a significant challenge. Successful antiretroviral therapy is dependent on sustaining high levels of adherence. Long-acting antiretroviral therapies have the potential to simplify anti-HIV dosing demands, which could provide meaningful improvements in adherence to prescribed therapies. Increased adherence to combination antiretroviral regimens has been associated with improved immunologic and virologic response, reduction in the emergence of HIV-resistance, and lower AIDS-related morbidity and mortality.

GSK3732394 could provide meaningful improvement in the lives of patients living with HIV. This novel recombinant protein is composed of three independent and distinct biological inhibitors of HIV-1, which may act synergistically with respect to potency and resistance and as a long-acting agent that can be administered subcutaneously. The projected profile of the compound suggests minimal cross-resistance with currently available ARV therapies, and with once-per-week dosing, GSK3732394 may improve adherence. As a large protein, many of the complications inherent with orally administered small molecules, including drug-drug interactions and food restrictions, may be mitigated. Finally, GSK3732394 may have the added convenience of being able to be self-administered at home; a necessary feature for a parenteral therapy targeting stable-switch patients.

The development plan for GSK3732394 is to investigate the drug as a mono-entity (with three mechanisms of action within a single compound), as well as part of a long-acting combination regimen.

The current study is a double-blind (sponsor-unblinded), randomized, placebo-controlled, two-part, first-time-in-human (FTIH) single- and multiple-ascending dose study to assess the safety, tolerability, and pharmacokinetic/pharmacodynamic attributes of GSK3732394. The inclusion of healthy participants enhances the safety of the trial by allowing the Sponsor to understand the potential immunologic effects of the compound, such as impact on the number or function of cluster of differentiation (CD)4+ T-cells and the impact of anti-drug antibodies on the pharmacokinetics of GSK3732394, before the compound is introduced to immune-compromised patients infected with HIV. The data gathered in this study will enable further clinical development of GSK3732394 in HIV-infected study participants.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To assess the safety and tolerability of single and multiple doses of GSK3732394 in healthy participants.	GSK3732394 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 predose values
Secondary	
To describe the pharmacokinetic (PK) profile of single and multiple doses of GSK3732394 in healthy participants.	Derived PK parameters for GSK3732394, as data allow: • Part 1 (single dose): $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, tlag, C_{last}, t_{last}, $t_{1/2,}$CL/F • Part 2 (Repeated once weekly [QW] dosing): ○ First week: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, t_{max}, t_{lag} ○ Last week: $AUC_{(0-\tau)}$ C_{max}, t_{max}, $C\tau$, $t_{1/2,}$ CL/F.
To examine dose proportionality following single and multiple doses of GSK3732394, as data allow.	PK linearity assessment using derived PK parameters, as data allow: • Part 1 (single dose): $AUC_{(0-\infty)}$, C_{max} • Part 2 (Repeat QW dosing): $AUC_{(0-\tau)}$, C_{max}, C_τ
To assess accumulation of GSK3732394 after multiple doses, as data allow.	Accumulation indices for PK parameters assessed across first and last doses of multiple dosing, as data allow: $RAUC_{(0-\tau)}$, RC_{max}, RC_τ.
To characterise CD4 receptor occupancy (RO) profile of single and multiple doses of GSK3732394.	Percent of CD4 RO.
To investigate the relationship between GSK3732394 exposures and CD4 RO.	C_{max}, C_{trough}, %RO
To characterise potential immunologic impact on, and immune responses to, healthy participants who receive a single or multiple dose(s) of GSK3732394.	• Change from baseline in CD3/CD4/CD8 and activated T-cell counts and percentages. • Change from baseline in CD4 median fluorescence intensity (MFI). • Titers and incidence of anti-GSK3732394 antibodies.

$AUC_{(0-t)}$ = Area under the plasma concentration time curve from zero (pre-dose) to t; $AUC_{(0-\infty)}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; C_{max}= Maximum observed concentration; t_{max}= Time of occurrence of C_{max}; t_{lag} = lag time; C_{last} = last observable concentration, t_{last} = time of last observable concentration; $t_{1/2}$ = Apparent terminal phase half-life; CL/F= Apparent clearance; $AUC_{(0-\tau)}$ = Area under the concentration-time curve at steady state within the dosing interval, C_τ (or C_{trough})= trough serum concentration; Accumulation ratios calculated as the ratio of Week 4 (last dose) to Week 1 (first dose) PK parameters: $RAUC_{(0-\tau)}$ = $AUC_{(0-\tau)}$ on Week 4 to $AUC_{(0-\tau)}$ on Week 1, RC_{max} = C_{max} on Week 4 to C_{max} on Week 1, RC_τ = C_τ on Week 4 to C_τ on Week 1.

Overall Design and Schematic:

This is a double-blind (sponsor-unblinded), randomized, placebo-controlled, single and multiple-ascending-dose study to evaluate the safety, tolerability and PK/pharmacodynamics (PD) of GSK3732394 in healthy participants. All doses will be administered subcutaneously. This study will be executed in 2 Parts.

In Part 1, the proposed dosing schedule is designed to investigate single ascending doses (SAD) of GSK3732394. In Part 2, the proposed dosing schedule is designed to investigate multiple ascending doses (MAD) of GSK3732394 administered weekly for four doses.

Dose escalation decisions, including the determination of the subsequent dose in Part 1, will be determined based on safety, pharmacokinetic and pharmacodynamic endpoints (receptor occupancy) and will be governed by a Safety and Dose Escalation Committee (SDEC).

Schematic:

PART 1 (6 GSK3732394 : 2 PBO)	SAD Cohort 1 (n = 8)	SAD Cohort 2 (n = 8)	SAD Cohort 3 (n = 8)	SAD Cohort 4 (n = 8)	SAD Cohort 5 (n = 8)	SAD Cohort 6 (n = 8)
Single SC Dose (C RO)	10mg (<10%)	*40mg* (≤25%)	*130mg* (≤70%)	*350mg* (≤90%)	*600mg* (≤95%)	*Up to 800mg or to repeat a prior dose*

PART 2 (6 GSK3732394 : 2 PBO)	MAD Cohort 1 (n = 8)	MAD Cohort 2 (n = 8)	MAD Cohort 3 (n = 8)
4 Subcutaneous Doses (C_{trough} RO) Administered Once Weekly (QW)	130mg (<70%)	*400mg* (≤90%)	*600mg* (≤95%)

Note: Doses shown in schematic are nominal and intended to demonstrate general concepts relating to factors of escalation as a base case. Dose escalation in Part 1 will be based on target receptor occupancy/exposure and governed by safety and PK stopping criteria. Transition to Part 2 will be after the completion of dosing and evaluation of SAD Cohort 4 participants and after the predicted exposure of the starting MAD dose is within that observed with SAD dosing – maximum predicted AUC, C_{max} not exceeding the average maximum observed in evaluated SAD cohorts (QW = once every week.).

Number of Participants:

In Part 1, a sufficient number of healthy adults will be screened to provide 8 participants for randomization within each of the SAD dosing cohorts. Overall, up to 48 participants will be included depending on the number of cohorts required.

In Part 2, a sufficient number of healthy adults will be screened to provide 8 participants for randomization within each of the MAD dosing cohort. Overall, up to 24 participants will be included depending on the number of cohorts required.

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

Treatment Groups and Duration:

Study participants will have a screening visit within 30 days prior to the first dose of GSK3732394 /Placebo (PBO).

In Part 1, participants will receive a single dose of GSK3732394 or PBO (6:2) on Day 1. Safety, PK and PD assessments will be performed at timepoints specified in the schedule of activity (SOA). Participants will remain in the clinic until the completion of the Day 14 procedures and will return to the clinic on Days 17, 21, and 24 for follow-up assessments, and an end-of-study evaluation on Day 28.

In Part 2, participants will receive doses of GSK3732394 or PBO (6:2) given at anticipated weekly intervals. Participants will remain in the clinic until the completion of the Day 35 procedures and will return to the clinic on Days 39, 42 and 46 for follow-up assessments, and an end-of-study evaluation on Day 49.

Duration of participation through follow-up may be longer if actual PK parameters differ significantly from predicted values (e.g. if half-life is significantly longer than the predicted); but will not exceed five half-lives.

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.

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. Vital signs
2. 12 lead electrocardiogram (ECG)
3. PK/PD sampling

Note: The timing of the assessments should allow blood draws to occur at the exact nominal time.

- The Institutional Review Board/ Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- 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.
- For serum biomarkers, baseline is defined as Day -1 post-randomization.

Table 1 SCREENING AND FOLLOW-UP/EARLY DISCONTINUATION ASSESSMENTS (Part 1 and Part 2)

Procedure	**Screening** (up to 30 days prior to Day 1) [1]	**Follow-up/Early Discon Visit** (~28 days post last dose)	***Notes***
			Follow-up Visit to occur approximately 28 days after last study drug administration or 5 half-lives (as determined from Part 1 PK data), whichever is longer.
Outpatient Visit	X	X	
Informed Consent	X		
Inclusion and Exclusion Criteria	X		
Demography	X		
Medical History	X		
Full Physical Examination (Including Height and Weight at the screening visit)	X		*Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).*
Target/Brief Physical Examination		X	
12-lead ECG	X	X	• *Triplicate ECGs will be used to determine participant eligibility at screening.* • *Additional tests may be performed by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Vital signs	X	X	
Urine Drug Screen	X		
Alcohol Screen	X		
Cotinine Screen	X		
Pregnancy Test	X	X	
HIV, Hep B and Hep C Screen	X		
Tuberculosis Test	X		
Laboratory assessments	X	X	
Pharmacokinetic sample		X	
Pharmacodynamic sample		X	
Anti- GSK3732394 antibodies		X	
Adverse Event Review	X	X	*The collection of SAEs will be from the screening visit to the end of the study*
Concomitant Medication Review	X	X	

1. Screening must be performed within 30 days prior to receiving the dose of GSK3732394/PBO on Day 1

Table 2 Part 1 - All Cohorts Inpatient Days -1 to Day 14

Procedure	Day																						
	Day 1									2	3	4	5	6	7	8	9	10	11	12	13	14	
	Day -1	Pre-dose	0 h	0.5 h	1 h	2 h	4 h	8 h	12h	24h	48h	72h	96h	120h	144h	168h	192h	216h	240h	264h	288h	312h	
Admission to Unit	X																						
Discharge from Unit																						X	
Urine Drug Alcohol/Screen/Cotinine	X																						
Brief Physical Exam	X									X						X						X	
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X						X		X	X						X						X	
Pregnancy Test	X																						
Meals	*Per site usual practice*																						
Laboratory assessments[1]	X									X	X		X			X			X			X	
Randomization		X																					
Drug administration			X																				
Pharmacokinetic sample[2]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacodynamic sample[2]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Antidrug Antibody sample	X														X			X				X	
Biomarker sample[3]	X																						
Urine sample[4]	X		X																				
SAE/AE Review[5]	<==========																						==========>
Con Med Review	<==========																						==========>

1. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
2. The number of PK and PD sampling time points may be reduced/extended in subsequent dosing groups once human PK data are available from initial SAD dosing cohorts. An aliquot of the PK serum sample will be used for GSK3732394-related material (serum metabolites) identification.
3. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
4. Urine will be collected at Day -1 (10mL) and for 24 hours after dose administration for GSK3732394-related material identification in the highest dose cohort only. Details for urine collection and interval is included in the SRM.
5. To include assessment of injection site(s) as appropriate (see also Section 3.3.1 and Section 8.1, and the SRM).

Table 3 Part 1 - Outpatient Visit Days 17, 21, 24, 28

Procedure	Day			
	17	21	24	28[1, 2]
Brief Physical Exam	X	X	X	X
Vital signs	X	X	X	X
12-lead ECG	X			X
Pregnancy Test				X
Laboratory assessments[3]	X	X	X	X
Pharmacokinetic sample[4,5]	X	X	X	X
Pharmacodynamic sample[4,5]	X	X	X	X
Antidrug Antibody sample		X		X
Biomarker sample[6]				
Adverse Event Review[7]	<==========			==========>
Con Med Review	<==========			==========>

1. In the event of terminal half-life longer than predicted, PK/PD and laboratory assessments will occur every four days until an estimated 5 half-lives have elapsed
2. For participants with no ongoing AEs or Vital Sign/Laboratory measures of clinical concern at Day 28 Visit, these procedures and those listed in Table 1 Screening and Follow-up/Early Discontinuation" for Follow-up/Early Discontinuation Visit (~28 days post last dose) may be considered the same.
3. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
4. An aliquot of this PK serum sample will be used for GSK3732394-related material (serum metabolites) identification.
5. PK samples collection on Days 17, 21 and 24 are conditional on the PK assessment at up to Day 7 during the conduct of the study and may be adjusted as data become available.
6. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
7. To include assessment of injection site(s) as appropriate (see also Section 3.3.1 and Section 8.1, and the SRM).

Table 4 Part 2 - All Cohorts Inpatient Days -1 to Day 17

Procedure	Day																												
	Day -1	Day 1								2	3	4	5	6	7	8		9	10	11	12	13	14	15		16	17
		Pre-dose	0 h	0.5 h	1 h	2 h	4 h	8 h	12h	24h	48h	72h	96h	120h	144h	Pre-dose	0 h	24h	48h	72h	96h	120h	144h	Pre-dose	0 h	24h	48h
Admission to Unit	X																										
Urine Drug/ Cotinine/Alcohol Screen	X																										
Brief Physical Exam	X									X					X								X				
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
12-lead ECG	X						X		X	X	X					X								X			
Pregnancy Test	X																										
Meals	*Per site usual practice*																										
Laboratory assessments[1]	X									X	X		X			X		X		X				X		X	
Randomization		X																									
Drug administration			X														X								X		
Pharmacokinetic sample[2]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Pharmacodynamic sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Antidrug Antibody sample	X															X								X			
Biomarker sample[3]	X																										
Urine sample[4]	X																										
Adverse Event Review[5]	<==========																										==========>
Con Med Review	<==========																										==========>

1. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
2. An aliquot of the PK serum sample will be used for GSK3732394-related material (serum metabolites) identification. Refer to the windows allowance agreement attached to the SRM for timing of trough samples to be drawn on non-dosing days.
3. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
4. Urine will be collected at Day -1 (10mL) and for 24 hours after dose administration for GSK3732394-related material identification after the 4th MAD dose. Details for urine collection and interval is included in the SRM.
5. To include assessment of injection site(s) as appropriate (see also Section 3.3.1 and Section 8.1, and the SRM).

Table 5 Part 2 - All Cohorts Inpatient Days 18 to Day 35

Procedure	Day																								
	18	19	20	21	22								23	24	25	26	27	28	29	30	31	32	33	34	35
	72h	96h	120h	144h	Pre-dose	0h	0.5h	1h	2h	4h	8h	12h	24h	48h	72h	96h	120h	144h	168h	192h	216h	240h	264h	288h	312h
Brief Physical Exam				X[5]									X						X						X
Vital signs	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X			X					X		X	X						X			X			X
Pregnancy Test																									X
Meals	*Per site usual practice*																								
Laboratory assessments[1]	X				X								X				X		X			X			X
Drug administration						X																			
Pharmacokinetic sample[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamic sample	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antidrug Antibody sample					X														X						X
Biomarker sample[3]																									
Urine sample[4]						X																			
Discharge from unit																									X
Adverse Event Review[5]	<==========																								==========>
Con Med Review	<==========																								==========>

1. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
2. An aliquot of the PK serum sample will be used for GSK3732394-related material (serum metabolites) identification. Refer to the windows allowance agreement attached to the SRM for timing of trough samples to be drawn on non-dosing days.
3. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms.
4. Urine will be collected for 24 hours after dose administration for GSK3732394-related material identification after the fourth (4th) MAD dose only.
5. To include assessment of injection site(s) as appropriate (see also Section 3.3.1 and Section 8.1 and the SRM).

Table 6 Part 2 - Outpatient Visits Days 38, 42, 46, 49

Procedure	Day			
	38	42	46	49[1]
Brief Physical Exam	X	X	X	X
Vital signs	X	X	X	X
12-lead ECG	X			X
Pregnancy Test				X
Laboratory assessments[2]	X	X	X	X
Pharmacokinetic sample[3]	X	X	X	X
Pharmacodynamic sample	X	X	X	X
Antidrug Antibody sample		X		X
Biomarker sample[4]				
Adverse Event Review[5]	<==========			==========>
Con Med Review	<==========			==========>

1. In the event of terminal half-life longer than predicted from SAD data, PK/PD and laboratory assessments will occur every four days until an estimated 5 half-lives have elapsed.
2. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
3. An aliquot of the PK serum sample will be used for GSK3732394-related material (serum metabolites) identification. Refer to the windows allowance agreement attached to the SRM for timing of trough samples to be drawn on non-dosing days.
4. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
5. To include assessment of injection site(s) as appropriate (see also Section 3.3.1 and Section 8.1 and the SRM).

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker 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) and to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments 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. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF

3. INTRODUCTION

3.1. Study Rationale

This is a double-blind (sponsor-unblinded), randomized, placebo-controlled, first-time-in-human (FTIH) study in a combined single-ascending and multiple-ascending dose protocol to assess the safety, tolerability, and pharmacokinetic/pharmacodynamic attributes of GSK3732394 in healthy participants. The data gathered in this study will enable further clinical development of GSK3732394 in HIV-infected patients.

3.2. Background

With the introduction of effective combination therapies, Acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality has declined significantly and, in many parts of the world, human immunodeficiency virus (HIV)-infection has been transformed into a treatable chronic condition. Despite the availability of a number of potent and safe antiretroviral agents (ARVs) across different therapeutic classes and the availability of one pill per day regimens, the burden of lifetime daily dosing remains a significant challenge. Successful antiretroviral therapy is dependent on sustaining high levels of adherence. Long-acting antiretroviral therapies have the potential to simplify anti-HIV dosing demands, which could provide meaningful improvements in adherence to prescribed therapies. Increased adherence to combination antiretroviral regimens has been associated with improved immunologic and virologic response, reduction in the emergence of HIV-resistance, and lower AIDS-related morbidity and mortality.

GSK3732394 is a novel biologic with three distinct, non-overlapping mechanisms to prevent HIV-1 viral entry. It is composed of an anti-CD4 adnectin, an anti-N17 adnectin, and a peptide inhibitor. Adnectins are derived from the 10th type III domain of the human fibronectin protein. They are small (~12kDa), compact proteins without disulfide bridges and are monomeric in nature. Adnectins are part of the immunoglobulin superfamily, and although there is little sequence similarity, the structure of an adnectin resembles an antibody variable domain. Thus, adnectins possess binding loops akin to the complementarity determining region (CDR) of an antibody, which can be altered to bind to a target of interest.

Specifically, the αCD4 adnectin binds to domains 2 and 3 of the cellular CD4 receptor, preventing necessary conformational change within the virus that allows for effective

viral entry into the host CD4+ T-cell, thereby inhibiting an early step in the viral replication lifecycle. While the anti-CD4 component of GSK3732394 works in a similar manner to ibalizumab, a recently approved antiretroviral monoclonal antibody that targets Domain 2 of the CD4 receptor, the CD4 receptor binding sites for the two molecules are not the same. The αN17 adnectin targets the α-helical N17 region of gp41 and the peptide inhibitor targets gp41 upstream of the N17 adnectin. The peptide inhibitor was designed to bind to the same α-helical region as enfuvirtide. The αN17 adnectin and the peptide inhibitor have similar mechanisms of action in that they both block the formation of the 6-helical bundle required for virus fusion. At the N-terminal part of GSK3732394 is a human serum albumin molecule (HSA), which decreases the antiviral EC50 by about 10-fold, but significantly enhances the PK of the compound.

Pre-clinical models have demonstrated GSK3732394 is active against most HIV-1 subtypes. The *in vivo* efficacy of GSK3732394, as a mono-entity, was comparable to a highly active anti-retroviral therapy (HAART) regimen through one-month of dosing in a humanized mouse model of HIV-1 infection [GlaxoSmithKline Document Number 2017N344293_00]. The potency and efficacy of the molecule is driven by the action of the αCD4 adnectin binding to its target. Not only does this function as a specific inhibitor of gp160 bound to the same CD4 molecule, it synergizes the potency of the anti-gp41 inhibitors (both the adnectin and peptide) by (1) greatly increasing its local concentration at the site of action and (2) allowing it to inhibit gp160 that are bound to other CD4 molecules. This ability to work *in trans* is the reason why high potency can be obtained at low receptor occupancy (RO) on CD4. For instance, *in vitro* studies showed that an RO of ~2.7% of bound CD4 molecules results in an EC90 for GSK3732394.

The projected profile of the compound suggests minimal meaningful cross-resistance with currently available ARV therapies. This includes other entry inhibitors, as no cross resistance was observed against maraviroc. Also, although the isolated peptide in GSK3732394 does exhibit some cross-resistance with enfuvirtide, in the context of the full length GSK3732394, minimal cross-resistance is observed against enfuvirtide-resistant viruses. A similar observation is made with the αCD4 adnectin piece from GSK3732394 and ibalizumab, which could share resistance pathways. However, in the context of GSK3732394, no cross-resistance is observed. Pre-clinical pharmacokinetics support the consideration of GSK3732394 as a long-acting agent that can be self-administered subcutaneously. As a large protein, many of the complications inherent with orally administered small molecules, including drug-drug interactions and food restrictions, may be mitigated. Taken together, these data support continuing compound development.

Following its successful evaluation in healthy subjects, GSK3732394 would proceed into testing in HIV-infected patients. The transition from healthy participants to HIV-infected participants means that, if CD4 binding is maintained, there will be the additional binding of the anti-N17 and gp-41 components of the compound to the available HIV virions, which is only possible in infected persons. Given that CD4 counts are generally lower in infected patients, the CD4 RO established in healthy participants should either be maintained or higher in HIV-infected patients. Thus, with the maintained or improved CD4 binding and the additional N17 and gp-41 binding, it is expected that doses resulting in targeted ROs in healthy participants should be efficacious in HIV-infected patients.

Detailed information relating to non-clinical pharmacology, safety pharmacology, pharmacokinetics and metabolism, toxicology and other pre-clinical data with GSK3732394 can be found in the GSK3732394 Investigator's Brochure (IB) (GlaxoSmithKline Document Number 2018N358742_00).

3.3. Benefit/Risk Assessment

This section outlines the risk assessment and mitigation strategy for this protocol. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3732394 may be found in the Investigator's Brochure (GlaxoSmithKline Document Number 2018N358742_00).

The main safety concerns with GSK3732394 administration to humans are based on theoretical risks relating to the subcutaneous injection of a protein based biologic agent and include immunogenicity, allergic reactions, and injection site reactions. In addition, reduction in CD4+ expression / count has been noted in preclinical studies with repeated dosing of GSK3732394 and with other investigational biologics which target CD4+ T-cells (e.g. keliximab and clenoliximab).

Consistent with Sponsor guidance for early phase studies, GSK3732394 will be administered in a hospital-based in-patient facility, with sufficient overnight facilities and emergency care capabilities.

To minimize the risk of the initial human administration of GSK3732394, a sentinel dosing strategy will be utilized in the SAD cohorts: one (1) participant will receive GSK3732394 and one (1) participant will receive PBO. After the Sponsor Medical Monitor and Primary Investigator have reviewed the safety data through 48 hours post-dose, the remaining participants from that cohort will be dosed. This 48-hour dosing stagger may be reduced following Cohort 1 if there are no safety or tolerability concerns.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3732394 (also refer to Clinical Investigator's Brochure (IB, GlaxoSmithKline Document Number 2018N358742_00)		
CD4+ cell reduction / Impairment in Immune Function	In the one-month GLP toxicity study (IB Section 4, GlaxoSmithKline Document Number 2018N358742_00), conducted in hCD4 transgenic mice, a decrease in the absolute and percentage CD4+ T-cells was seen at GSK3732394 doses of 50 and 500 mg/kg (human equivalent dose ~284 mg and ~2,835 mg, respectively). This reduction was fully resolved by the end of the post-treatment period (Day 57) in mice dosed at 50 mg/kg and partially resolved in mice dosed at 500 mg/kg. Similar effects on CD4+ T cell count were observed in the one-month GLP TDAR study (CIB Section 4, GlaxoSmithKline Document Number 2018N358742_00); also conducted in hCD4 mice. In an ELISpot assay, conducted in PBMCs from human donors exposed to concentrations of GSK3732394 up to 100 µg/mL (projected C_{max} at the equivalent human dose of ~1,600 mg), there were no dose-dependent changes in MHC Class II-restricted IFN-γ response to a pool of peptide antigens from common viruses (IB Section 4, GlaxoSmithKline Document Number 2018N358742_00). However, in the TDAR study, there was a decrease in anti-KLH IgG antibody response was observed at 500 mg/kg; antibody response returned to baseline during the 8-week post-treatment period. There was no observed adverse effect on antibody response in hCD4 mice dosed at 50 mg/kg. Overall, preclinical results suggest reduction in CD4+ T-cell count is likely to precede measurable impairment in T-cell-dependent immune function. Based on current predictions, it is estimated that CD4+ T-cell reduction could be evident at a forecast C_{max} of 93.9 µg/mL (human equivalent exposure to 50 mg/kg in mice) following repeated dosing/prolonged exposure.	• *Eligibility is limited to healthy adult participants with no medical history of immune compromise.* • *Participants will be excluded if they have screening absolute CD4+ T-cell counts <500 cells or CD4 percent (CD4%) outside of the normal range for the reference laboratory (32% to 64%). See Section 6.2.* • *CD3/CD4/CD8 and activated T-cell counts and percentages will be monitored throughout the study.* • *Dosing will be stopped if two participants experience confirmed Grade 2 reductions in absolute CD4+ T-cell count (Division of AIDS [DAIDS] Criteria v 2.1; Appendix 6, Section 12.6) or have confirmed >25% reduction in baseline %CD4, following an injection of GSK3732394.* • *Dosing will also be stopped if one participant experiences a confirmed Grade 3 reduction of CD4+ T-cell count (Appendix 6, Section 12.6), or have a confirmed drop in CD4% >40%, see Section 8.1.*
Immunogenicity	As with any protein- or peptide-based therapy, GSK3732394 has the potential to induce antidrug antibodies. The chemical structure and characteristics of GSK3732394 suggest the compound has medium to high risk of inducing anti-drug antibodies (immunogenicity) in humans. Anti-GSK3732394 antibodies have been observed in nonclinical studies in cynomolgus monkeys and human CD4 (hCD4) mice. Although ADA responses were also noted in the GLP toxicology study in hCD4 mice treated with 50 or 500 mg/kg every other day for one month (IB Section 4, GlaxoSmithKline Document Number 2018N358742_00) in general, systemic exposure and PD (RO) were maintained throughout the dosing period. Animal studies are generally not predictive of immunogenicity and *sequelae* related to immunogenicity in humans.	*The emergence of anti-GSK3732394 antibodies will be actively monitored and characterized during the 207863 study, including the impact of ADAs on drug clearance / pharmacokinetics of the compound. See Section 9.8.1.*
Cytokine Release	In an *in vitro* cytokine release assay (CRA, IB Section 4, GlaxoSmithKline Document Number	• *Participants will be closely monitored in an in-patient*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Syndrome	2018N358742_00), a dose-responsive IL-8 cytokine release was observed in human PBMCs incubated with GSK3732394 (starting at concentrations as low as 1.0 µg/mL). No GSK3732394-related changes were observed with IL-2, IL-6, IL-10, IFN-γ or TNFα. Results of CRA assays are often not well-correlated with the human experience. The physical properties and biological target of GSK3732394 suggest the potential for GSK3732394 to induce hyper-immune activation and clinically significant cytokine release is believed to be quite low.	*unit throughout the dosing of GSK3732394 and for 14 days of post-dosing follow-up. On-site study personnel qualified to manage acute cases of serious allergic reactions, see Section 8.1.1.1.* • *Discontinuation criteria are provided in Section 8.1.* • *Percent activated CD4 cells will be monitored routinely.* • *Biomarkers of immune reaction/activation will be collected and analyzed in participants exhibiting signs and symptoms consistent with hypersensitivity. See Section 9.8.1.*
Local injection site reactions	Among hCD4+ transgenic mice treated as part of the one-month GLP toxicity study, there was a slight increase in the incidence and/or severity of minimal to mild inflammation observed in the injection site dermis and/or subcutis of animals dosed with GSK3732394 versus vehicle. These changes were reversible.	*Injection sites will be actively monitored for adverse reactions following administration of GSK3732394, as part of routine physical assessment. Adverse reactions will be recorded within the safety database as adverse events as appropriate (see also Section 8.1.1).*
Drug interactions	No formal drug-interaction studies have been conducted with GSK3732394. However, because of GSK3732394's biological format the potential for drug/drug interactions is low.	*Appropriate exclusion criteria relating to the use of concurrent medications throughout the study are provided in Section 6.2.*

3.3.2. Benefit Assessment

This is a study in healthy participants and as such there is no expected benefit to administration of GSK3732394. Participation in this study may contribute to the development of new therapies for HIV. There may be benefit to individual participants from the medical evaluations and assessments that could identify conditions that the participant was previously unaware of.

3.3.3. Acute Monitoring in FTIH Studies

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 and with immediate access to hospital facilities for the treatment of medical emergencies. In addition, a standard battery of safety related assessments will be actively monitored. Refer to the SOA for safety assessments.

3.3.4. Overall Benefit : Risk Conclusion

To date, GSK3732394 has not been administered to human participants. Given the non-clinical profile to date, the overall risk to participants at the proposed single and multiple doses of GSK3732394 is predicted to be low. Routine safety and tolerability will be evaluated from reported adverse events (AEs), scheduled physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff.

The study will be conducted in a hospital-based unit or unit with immediate access to hospital facilities for the treatment of medical emergencies. The in-house periods as detailed in the Time and Events table will allow for continuous medical monitoring for all subjects following the first dose in each treatment group. Subjects will only be discharged from the unit 14 days post-dosing, if the Investigator deems it safe to do so.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK3732394 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of continued need.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To assess the safety and tolerability of single and multiple doses of GSK3732394 in healthy participants.	GSK3732394 safety parameters: adverse events; post-baseline values and changes over time of clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from pre-dose values
Secondary	
To describe the pharmacokinetic (PK) profile of single and multiple doses of GSK3732394 in healthy participants.	Derived PK parameters for GSK3732394, as data allow: • Part 1 (single dose): $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, t_{lag}, C_{last}, t_{last}, $t_{1/2}$,CL/F • Part 2 (Repeated QW dosing): ○ First week: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, t_{max}, t_{lag} ○ Last week: $AUC_{(0-\tau)}$ C_{max}, t_{max}, $C\tau$, $t_{1/2}$, CL/F.
To examine dose proportionality following single and multiple doses of GSK3732394, as data allow.	PK linearity assessment using derived PK parameters, as data allow: • Part 1 (single dose): $AUC_{(0-\infty)}$, C_{max} • Part 2 (Repeat QW dosing): $AUC_{(0-\tau)}$, C_{max}, C_τ
To assess accumulation of GSK3732394 after multiple doses, as data allow.	Accumulation indices for PK parameters assessed across first and last doses of multiple dosing, as data allow: $RAUC_{(0-\tau)}$, RC_{max}, RC_τ.
To characterise CD4 receptor occupancy (RO) profile of single and multiple doses of GSK3732394.	Percent of CD4 RO.
To investigate the relationship between GSK3732394 exposures and CD4 RO.	C_{max}, C_{trough}, %RO
To characterise potential immunologic impact on, and immune responses to, healthy participants who receive a single or multiple dose(s) of GSK3732394.	• Change from baseline in CD3/CD4/CD8 and activated T-cell counts and percentages. • Change from baseline in CD4 median fluorescence intensity (MFI). • Titers and incidence of anti-GSK3732394 antibodies.
Exploratory	
To model the relationship between GSK3732394 exposures and CD4 RO.	Estimating parameters descriptive of the relationship including Concentration resulting in 50% RO (EC50), as data allow.
To explore the correlation between GSK3732394 exposure and observed safety outcomes.	Occurrence of AEs /laboratory abnormalities and corresponding plasma concentrations / doses of GSK3732394.
To explore serum and urine metabolite(s) investigations of GSK3732394.	Identification of any compound-related degradants

$AUC_{(0-t)}$ = Area under the plasma concentration time curve from zero to t; $AUC_{(0-\infty)}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; C_{max}= Maximum observed concentration; t_{max}= Time of occurrence of C_{max}; t_{lag} = lag time; C_{last} = last observable concentration, tlast = time of last observable concentration; $t_{1/2}$ = Apparent terminal phase half-life; CL/F= Apparent clearance; $AUC_{(0-\tau)}$ = Area under the concentration-time curve at steady state within the dosing interval, C_τ= trough serum concentration; Accumulation ratios calculated as the ratio of Week 4 (last dose) to week 1 (first dose) PK parameters: $RAUC_{(0-\tau)}$ = $AUC_{(0-\tau)}$ on Week 4 to $AUC_{(0-\tau)}$ on Week 1, RC_{max} = C_{max} on Week 4 to C_{max} on Week 1, RC_τ = C_τ on Week 4 to C_τ on Week 1.

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 1, 2 Part, double-blind (sponsor-unblinded), randomized, placebo-controlled, single and multiple-ascending-dose study to evaluate the safety, tolerability and pharmacokinetics/pharmacodynamics of GSK3732394 in healthy participants. Up to approximately 72 healthy participants will be randomized in Part 1 (SAD, n=48) and Part 2 (MAD, n=24). The total number of cohorts in the SAD will be six and the total number of cohorts in the MAD will be a maximum of three. All dosing and post-dosing follow-up (through 14 days post-dosing) will be conducted in a hospital based inpatient clinical trial unit. A final follow-up visit will take place at least 14 days after discharge from the inpatient unit (approximately 28 days post-last dose). Time & Events (T&E) Schedule of Activities tables are included in the Schedule of Activities section of this protocol (Section 2).

A summary of the overall study design, including proposed doses, sample size, and order, is presented in Table 7 and Table 8.

Table 7 Part 1 (Base case)

Cohort	Target CD4 Receptor Occupancy (RO)		Forecast Dose[1] (mg)	Forecast Pharmacology
	Min	Max		Ibalizumab based leveraging
1	<10%	<60%	10	No activity
2	≤25%	≤80%	40	Some minimal activity
3	≤70%	≤95%	130	Sparingly active
4	≤90%	≤98%	350	Active (if target mediated drug disposition [TMDD], likely observed)
5	≤95%	≤100%	600	Active (if TMDD, likely observed)

[1] Doses listed are proposed/base case. After Cohort 1, actual doses will be decided based on PK, RO, and safety data from prior cohorts.
Note: An additional cohort (6) of up to 800mg or to repeat a prior dose may be included (See Section 5.5.2).

Table 8 Part 2 (Base case)

MAD (6 active: 2 PBO)	Cohort 1 (n= 8)	Cohort 2 (n= 8)	Cohort 3 (n= 8)
Four weekly SC doses[1]	130mg	400mg	600mg

[1] Doses listed are proposed/base case. Actual doses will be decided based on PK, RO, and safety data from prior cohorts in Part 1 and Part 2.

As described in detail below, the proposed dosing schedule is designed to investigate single doses of GSK3732394 in Part 1 and then, at a suitable cross-over point, begin repeated once-weekly dosing of GSK3732394 in Part 2.

Part 1 (SAD):

In Part 1, the proposed dosing schedule is designed to investigate SAD of GSK3732394 in healthy participants. All doses will be administered subcutaneously.

The SAD portion of the study will be conducted in six separate cohorts of eight healthy adult participants each. Each of the participants in the SAD cohorts will receive a single dose of blinded GSK3732394 or blinded PBO (GSK3732394 : PBO = 6:2, per their randomization assignment). Details of the starting dose and dose escalation can be found in Section 5.5.1 and Section 5.5.2, respectively. Dose escalation decisions, including the determination of subsequent doses in Part 1, will be determined by the Safety and Dose Escalation Committee (SDEC). See Section 5.5.5.

To conservatively assess safety, at the start of each of the SAD cohorts, 2 out of these participants will serve as sentinel participants with one receiving blinded GSK3732394 and the other receiving blinded PBO. The investigator may stagger dose administration time as needed for the sentinel participants. These sentinel participants will be followed clinically for 48 hours after dose administration to monitor for emergence of adverse events. If there are no safety concerns, in the judgment of the PI, on review of the 48-hour safety data (e.g. vital signs, ECGs, and adverse events) for the sentinel

participants, the remaining 6 participants will subsequently be administered either GSK3732394 or PBO, according to randomization schedules. The investigator may stagger dose administration time as needed. The 48-hour dosing stagger may be reduced following Cohort 1 if there are no safety or tolerability concerns (see Section 5.5.2, Section 5.5.3, and Section 5.5.4).

Part 2 (MAD):

In Part 2, the proposed dosing schedule is designed to investigate multiple ascending doses (MAD) of GSK3732394 in healthy participants administered weekly for a total of four doses. All doses will be administered subcutaneously.

Part 2 consists of up to three ascending repeat-dose cohorts (MAD Cohorts 1, 2, and 3), each with 8 participants (GSK3732394 : PBO = 6:2) who will receive four weekly doses of GSK3732394 or PBO on Days 1, 8, 15, and 22. Details of starting dose and dose escalations in Part 2 (MAD) can be found in Section 5.5.3.

The starting MAD dose will be a dose identified in the SAD that achieves mean RO at C_{trough} of at least 20%. The maximum dose in the MAD will not exceed that cleared in the SAD portion of the trial and will not be >9x the starting MAD dose. The predicted exposure (C_{max}) for the final MAD dosing per a given cohort (fourth dose) will not exceed the maximum exposure observed in SAD. The intermediate dose, used in MAD Cohort 2, will be approximately halfway between the starting and maximum doses administered in MAD Cohorts 1 and 3, respectively.

The start of the MAD investigation will be after completion of dosing and evaluation of SAD Cohort 4 participants and after the predicted exposures of MAD Cohort 1 are within that covered by exposures examined within the SAD portion of the trial – maximum predicted C_{max} (of any of the four doses administered to a MAD Cohort) not exceeding the average maximum observed in evaluated SAD cohorts. See Section 5.5.3.

Participants in both Part 1 and Part 2 will have a screening visit within 30 days prior to first dose and a follow-up visit 28 days after the last dose in both Part 1 (SAD) and Part 2 (MAD) of the study. Duration of study participation will be approximately 4 weeks for SAD participants and 7 weeks for MAD participants, unless the actual PK parameters differ significantly from predicted base case values.

5.2. Number of Participants

In Part 1, sufficient healthy adults will be screened into the study to provide approximately 8 participants per cohort. Overall, up to 48 participants will be included depending on the number of cohorts required.

In Part 2, sufficient healthy adults will be screened into the study to provide approximately 8 participants per cohort. Overall, up to 24 participants will be included depending on the number of cohorts required.

Participants will not be replaced if the reason for discontinuation from the study is due to a safety concern. If participants prematurely discontinue the study for non-safety

reasons, additional replacement participants may be enrolled at the discretion of the Sponsor. These replacement participants will be assigned to the same treatment sequence and same dose as the corresponding participant who prematurely discontinued from the study.

5.3. Participant and Study Completion

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 Schedule of Activities.

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

5.4. Scientific Rationale for Study Design

This first-time-in-human (FTIH) study will assess the safety, tolerability, and PK/PD attributes of GSK3732394 in healthy participants. The data gathered in this study will enable further clinical development of GSK3732394 including a Phase 2a proof-of-concept study in HIV-infected participants.

A healthy participant population is appropriate for this FTIH study. This will allow for robust data to be collected in a population free of confounding co-morbidities, concomitant medications, and other intrinsic and extrinsic factors that increase variability of these data. In addition, the preclinical safety profile of GSK3732394 supports evaluation in healthy participants.

In Part 1 (SAD), a flexible dose escalation design is planned. The starting dose selection is based upon preclinical safety, PK and PD data as described in Section 5.5.1. Dose escalation will be based on PK, PD and safety data from all prior cohorts. The dose escalation jumps between cohorts are projected to progressively decline from the previous dose of GSK3732394 and will not exceed 4-fold (see Section 3.3.1 and Section 5.5).

Transition to Part 2, the multiple ascending dose portion of the study, is dependent on clearance of exposures correlating with an anticipated therapeutic effect in humans (mean C_{trough} RO of at least 20% in Part 1). Subsequent dosing in Part 2 will only be administered if there is no identified dose-limiting toxicity identified at the corresponding dose in the SAD portion of the study (see Section 5.5.2, Section 5.5.3, and Section 5.5.4).

The inpatient observation period of at least 14 days (or at least 3 half-lives if longer) after the last dose provides an opportunity to ensure that adverse events have resolved or are resolving prior to discharge of participants from the inpatient unit. Additionally, the inpatient period provides a controlled environment that reduces the likelihood of participants engaging in routine daily activities that may result in adverse events or otherwise confound the safety evaluation of study treatment.

This study includes a PBO arm within each dosing cohort to allow for a valid evaluation of adverse events attributable to GSK3732394 versus those independent of investigational therapy.

5.5. Dose Justification

Human PK was forecast using allometric scaling of *cynomolgus* monkey IV and SC PK data. PK characteristics were identified using murine PK studies in transgenic humanized-CD4 mice investigating GSK3732394 PK at doses up to 500 mg/kg. These data support the human PK parameters allometrically predicted from the *cynomolgus* monkey and described linear PK and the absence of target mediated drug disposition (TMDD) whilst binding CD4.

A starting dose of 10 mg is proposed which compares conservatively across a variety of approaches used to evaluate safe starting doses. The chosen starting dose assumes the most potent response determined preclinically forecasting a C_{trough} CD4 receptor occupancy of <10%. The consequences of binding at this rate of occupancy suggests no CD4+ T cell reduction and no pharmacological activity. The subsequent dosing cohorts will target prespecified receptor occupancies allowing for flexibility in responding to emerging PK and pharmacological data.

Predicted Pharmacokinetics

GSK3732394 is predicted to have linear pharmacokinetics with an elimination half-life of approximately 50 hours. The evaluation of the preclinical data and the prediction process are detailed in the Clinical Pharmacology Review (GlaxoSmithKline Document Number 2018N365256_01). Briefly, the pharmacokinetics were allometrically scaled from observed *cynomolgus* PK which closely matched those of mice. There was no preclinical evidence of target mediated drug disposition. However, an FDA approved αCD4 monoclonal antibody (ibalizumab) has demonstrated TMDD within its preclinical and clinical data and these data have been used to anticipate, if TMDD should occur, at what doses this is likely to happen (when CD4 receptor occupancy is >90% for a period of time).

The predicted human PK have been used to forecast starting and subsequent doses (Table 9). These data will be assessed as PK data is acquired within the SAD. Attention will be paid to any emerging evidence of supra-proportional increases in exposure (although TMDD is not expected) and/or any extension in PK.

Table 9 Predicted parameters for a two-compartment PK model describing GSK3732394's human disposition

Parameter	Predicted Value	%CV[a]
Clearance (mL/hr/kg)	1.45	30
V1 (mL/kg)	58.6	20
Q2 (mL/hr/kg)	1.60	ND
V2 (mL/kg)	35.7	ND
KA (hr-1)	0.0778	20
F2	0.582	ND
ALAG2 (hr)	0.151	ND

[a] Assumed variability for human PK simulations
ND – not determined

5.5.1. Human Starting Dose Forecast

The 10 mg starting dose is forecast to cause trough CD4 receptor occupancy (RO) of 4% and maximal CD4 RO of 53%. The forecast is based on predicted human PK (based on cyno PK) and RO observed with GSK3732394 concentrations in transgenic hCD4 mice.

The starting dose of 10 mg is lower than the assessed thresholds [Table 10]:

1. It is lower (28.4-fold and 2.84-fold following application of a 10x safety factor) than the human allometric equivalent of the HED NOAEL (established at 50 mg/kg in hCD4 Tg mice)
2. It is lower (130.4-fold) than the NOAEL exposure matching based on $C_{max.}$
3. It is lower (83-fold) than the MABEL as calculated in vitro in hPBMCs.
4. It is lower (2-fold) than the MABEL as calculated in vivo in the Transcure HIV-infected mice.
5. It is lower (4.4-fold) than ibalizumab's molecular weight-adjusted minimally effective single dose of 1 mg/kg (equivalent to 44mg GSK3732394). The 10 mg starting dose for GSK3732394 also yields CD4 RO that is lower than that established with ibalizumab's minimally effective dose – where GSK3732394 predicted mean RO at C_{max} for 10 mg is 53% vs. ibalizumab at 1mg/kg C_{trough} is 50-70% RO.
6. It only exceeds (3.3-fold) the predicted dose for a human adult established within an *in vitro* anti-viral assay where the results have little relevance given that the assay assessed binding and anti-viral effects across the complete GSK3732394 compound, including the anti-N17 and peptide components. This effect can only be considered in the presence of HIV virus, not in non-HIV-infected persons.

Table 10 Summary of starting dose assessments ordered by technique

Approach	Predicted Dose Human Adult (mg)	PD-coverage (dose-fold) to 10 mg starting dose
HED with safety factor of 10x (50 mg/kg hCD4 mouse toxicology)	28.4	2.84-fold
NOAEL exposure matching (50 mg/kg hCD4 mouse toxicology)	1,304	130.4-fold
MABEL		
CD4 receptor occupancy *In vitro* 20% RO in hPBMCs	830	83-fold
Anti-viral effect *In vitro* Human trough equivalent to EC_{50} in NLRepRlic Virus in MT-2 cells	3.3	0.33-fold
In vivo Human trough equivalent to mouse trough associated with minimal effect in Transcure anti-viral experiment achieving 10% RO	20	2-fold
Other marketed products Equivalent (adjusting for molecular weights) to minimally effective dose of 1 mg/kg Ibalizumab	44	4.4-fold

Note: safety-fold coverage for predicted human exposure at 10 mg dose to NOAEL exposure in hCD4 mouse: Cmax (148-fold) and AUC (57-fold)

Safety Margins

Table 11 below lists the predicted safety cover for GSK3732394 at various planned doses in the SAD FTIH study and indicate that even with highest dose planned (800 mg), there is a ~2-fold margin for C_{max}:

Table 11 Projected mean GSK3732394 AUC, C_{max}, calculated C-average and C_{trough} following single doses of GSK3732394, with Fold Cover to hCD4 NOAEL exposures

Dose (mg)	Predicted Human Plasma Exposures				Safety Margins			
	AUC (µg.h/mL)	C_{max} (µg/mL)	C-average (µg/mL)	C_{trough} (µg/mL)	AUC	C_{max}	C-average	C_{trough}
10	57	0.6	0.3	0.09	57.2	147.7	200.1	349.7
40	228	2.5	1.4	0.38	14.3	36.9	50.0	87.4
130	741	8.3	4.4	1.23	4.4	11.4	15.4	26.9
350	1996	22.2	11.9	3.32	1.6	4.2	5.7	10.0
600	3422	38.1	20.4	5.70	1.0	2.5	3.3	5.8
800[1]	4562	50.8	27.2	7.59	0.7	1.8	2.5	4.4

Key:
NOAEL exposures in hCD4 transgenic mouse are:
AUC = 3,260 µg.h/mL; C_{max} = 93.9 µg/mL; calculated C-average = 67.9 µg/mL; C_{trough} at 48 h = 33.2 µg/mL
Safety margin = At mouse 50mg/kg NOAEL exposure parameter value/predicted human plasma exposure parameter
[1] An additional cohort of up to 800mg, or to repeat a previous dose, may be included as required

5.5.2. Dose Elevation Strategy

The dose elevation strategy applied the predicted PK and trough concentration – receptor occupancy relationship to predetermine target receptor occupancies for the ascending dose cohorts. The target receptor occupancies were chosen leading to minimize the jump magnitude between latter cohorts and optimised against a forecast dose-response relationship based on preclinical pharmacology. The PK – RO model was that defined from the hCD4 mouse data and extrapolated to human. The receptor occupancy consequences are described in Table 12 relative to ibalizumab anti-viral and CD4 data.

Table 12 The receptor occupancy consequences relative to ibalizumab anti-viral and CD4 data

Cohort	Target CD4 Receptor Occupancy (RO)		Forecast Dose (mg)	Forecast Pharmacology
	Min	Max		Ibalizumab based leveraging
1	<10%	<60%	10	No activity
2	≤25%	≤80%	40	Some minimal activity
3	≤70%	≤95%	130	Sparingly active
4	≤90%	≤98%	350	Active (if TMDD, likely observed)
5	≤95%	≤100%	600	Active (if TMDD, likely observed)

This escalation plan assumes an effective dose 90 (ED90) of ~400 mg allowing further escalation to 600 mg. The jump ratios between cohorts are: 4.0x, 3.5x, 2.9x and 1.7x. This allows characterization of the concentration-RO relationship for modelling and interpolation.

Based on ibalizumab-based leveraging of pharmacology, the first dose is forecast to be completely inactive. The second cohort is forecast to only achieve a scarce time-period where GSK3732394 levels would be forecast to be minimally pharmacologically active. The third cohort was chosen so that GSK3732394 levels would be above the minimal activity threshold with minimal duration at fully active levels. The fourth and fifth cohorts were chosen so that GSK3732394 would be at active levels with only the duration extending in the move from cohorts 4 to 5.

After each cohort, the data will be reviewed – the data consists of the PK, RO, relationship between PK and RO, and safety data. At each cohort dose review, a dose will be proposed that meets the RO requirements for the next dosing cohort. Dosing will be adjusted if it exceeds a 4-fold jump, if the PK is non-linear (as assessed by PK modelling), or if there are any observations that indicate the dose would carry a risk of safety concerns.

If there are no safety concerns, then the endorsement of the next cohort's dose can occur considering the PK and RO assessment:

1. If the PK is either: as predicted (cohort 1) and/or displays dose linearity (Cohort 2+)
2. If the RO is as predicted and follows the forecast PK-RO relationship

If either of these criteria are not met, then the following assessments should be made and endorsed by the sponsor and their review panel:

Pharmacokinetics

- If the PK displays non-linear characteristics i.e. TMDD or ADA, the PK data will be modelled to accurately predict the time course of the subsequent dose meeting the RO target.
- If the exposure caused by the subsequent dose increases by more than 4-fold, then a dose will be chosen to constrain exposure to a maximum predicted increase of 4-fold.

Receptor Occupancy

If the PK-RO relationship is not as forecast, then this will be re-evaluated using the available human data to anticipate:

- The ED_{90}
  - If ED_{90}>600mg, then adjust doses and cohorts, as needed and include an additional cohort with a maximum dose of 800mg as required.
  - If ED_{90}<600mg, then adjust doses and cohorts, as needed with a dose jump ≤4 times and including an intervening cohort, as required.

5.5.3. Transition to Multiple Ascending Dose Period

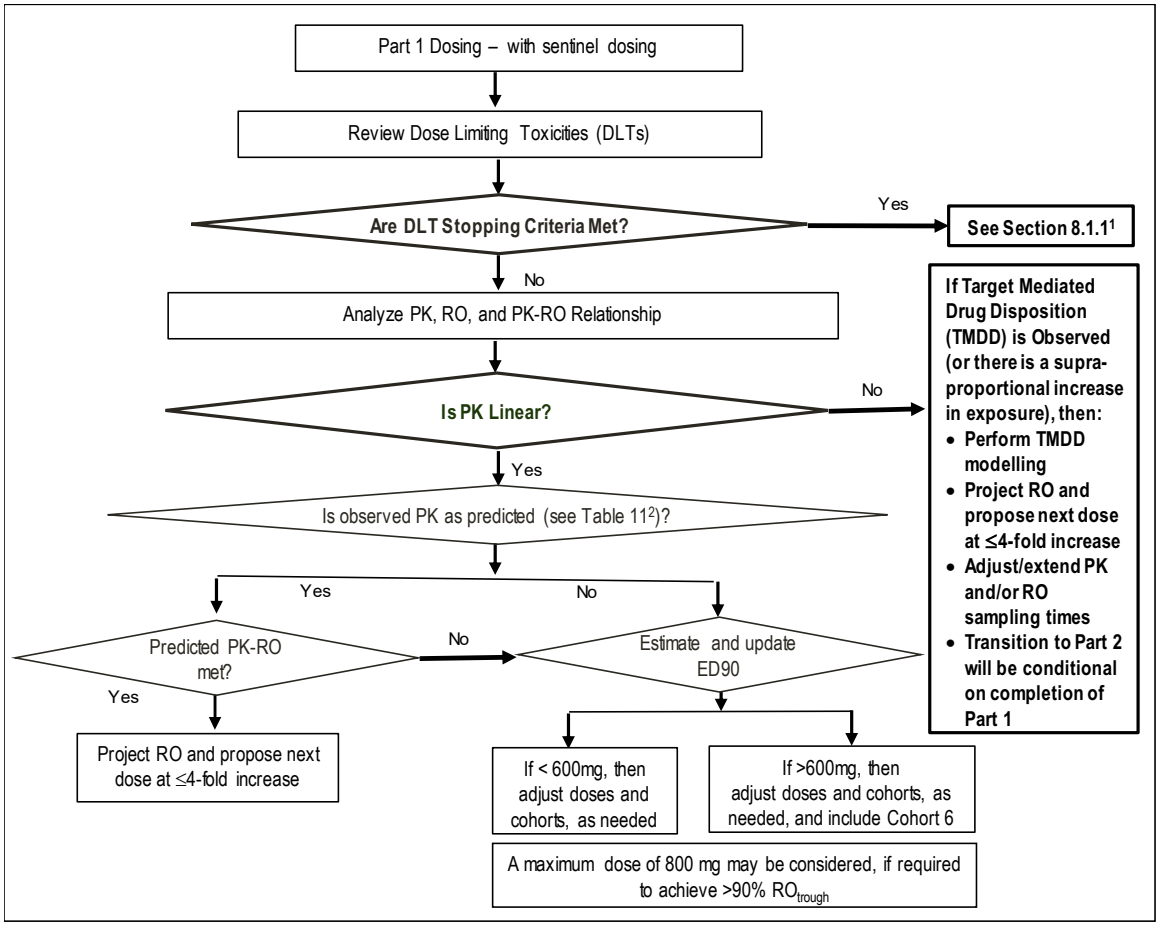
The starting dose in Part 2 (MAD) will be a dose identified in Part 1 (SAD) that achieves a mean RO at C_{trough} of at least 20%. The predicted exposure (C_{max}) for MAD doses will not exceed the maximum exposures observed in SAD and will not be >9x the starting MAD dose. The intermediate MAD dose will be approximately halfway between the starting and maximum MAD dose. If a mean RO at C_{trough} of at least 20%, is not achieved in Part 1 Cohorts 1 through 4; then Part 1 Cohort 5 and an additional Cohort (if needed) will complete prior to transitioning to Part 2 (MAD).

The start of the MAD investigation will be after completion of dosing and evaluation of SAD Cohort 4 participants and after the predicted exposure of the starting MAD dose is within that observed with SAD dosing – maximum predicted C_{max} not exceeding the average maximum observed in Part 1 cohorts.

Part 1 dose reviews will be performed if either the PK or PK-RO relationship deviates from that which is forecast. Schematics showing the decision flow-charts for Part 1 (SAD) escalation(s) (Figure 1) and the transition to Part 2 (MAD), with escalation strategy for Part 2 (Figure 2), are available in Section 5.5.4.

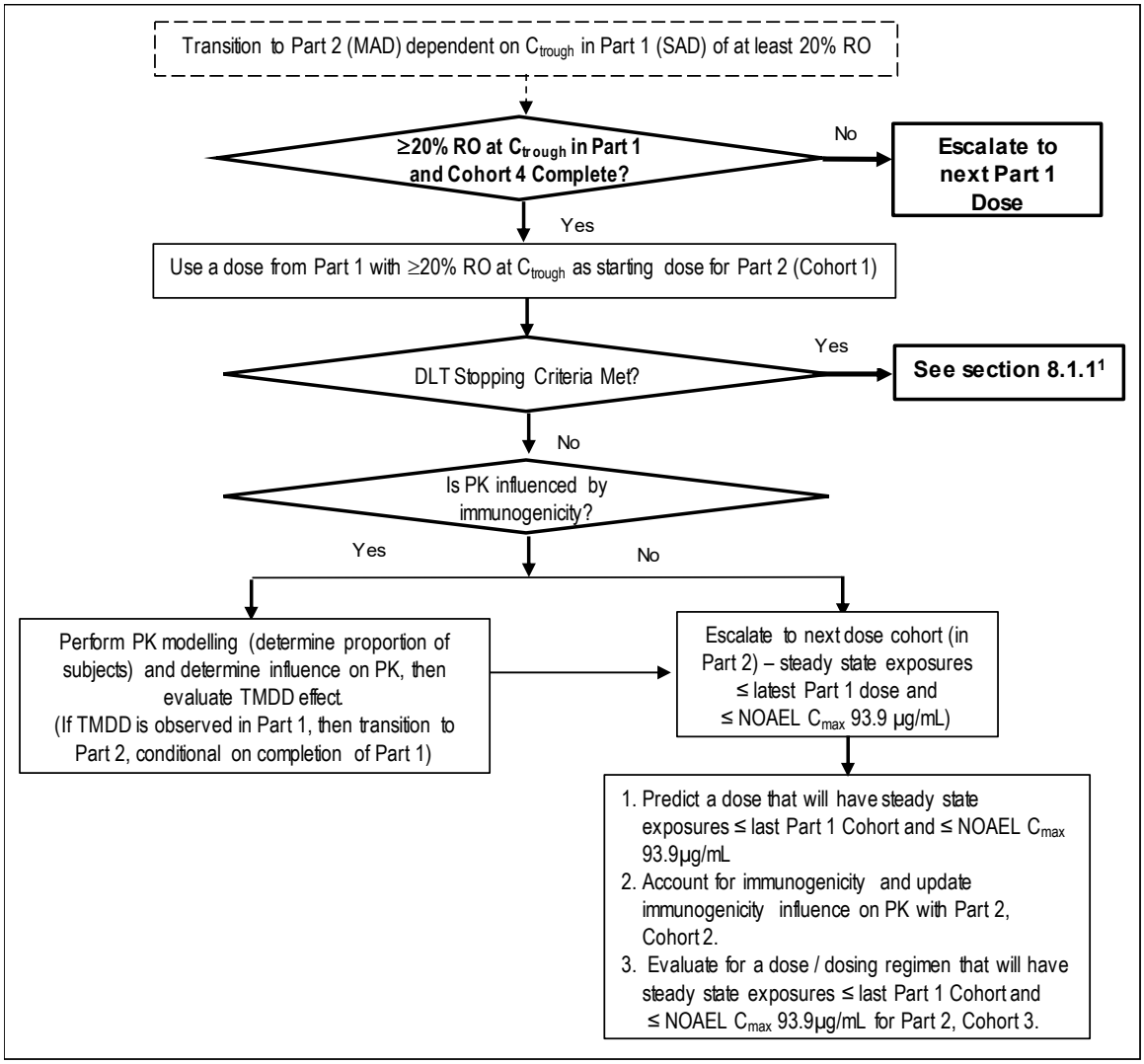
5.5.4. Dose Escalation Algorithms

Figure 1 Decision Flow for Dose Escalation(s) in Part 1



[1] See Section 8.1.1
[2] See Table 11

Figure 2 Decision Flow from Part 1 (SAD) to Part 2 MAD



[1] See Section 8.1.1

5.5.5. Human Safety and Dose Escalation Committee

This study will utilize a Safety and Dose Escalation Committee (SDEC) 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/PD data. The SDEC will meet when data are available from a minimum of four active treated participants through the Day 7 assessments in Part 1 and through the Day 29 assessments in Part 2. The blinding of personnel is discussed in Section 7.4. The construct and function of the SDEC will be documented in a Charter.

6. STUDY POPULATION

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

6.1. 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 50 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 medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. 3. Participants who are able to understand and comply with protocol requirements and timetables, instructions, and protocol-stated restrictions

WEIGHT
4. Body mass index within the range 19-30 kg/m^2 inclusive, in addition to a weight range of 50kg - 100kg.

SEX
5. Male and female healthy volunteers. **Male participants:** A male participant must agree to use contraception as detailed in Appendix 4 (Section 12.4) of this protocol during the treatment period and for at least 100 days after the last dose of study treatment and refrain from donating sperm during this period. **Female participants:** A female participant is eligible to participate if she is not pregnant (see Appendix 4 (Section 12.4), not breastfeeding, and at least one of the following conditions applies: • Not a woman of childbearing potential (WOCBP) as defined in (see Appendix 4 (Section 12.4), OR • A WOCBP who agrees to follow the contraceptive guidance in (see Appendix 4 (Section 12.4) during the treatment period and for at least 28 days prior to first dose, and 40 days after, the last dose of study treatment.

INFORMED CONSENT
6. Capable of giving signed informed consent as described in Appendix 1 (Section 12.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. 7. A signed and dated written informed consent must be completed prior to the participant's entry into the study.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or presence of cardiovascular, dermatological, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data. 2. Abnormal blood pressure (as determined by the investigator). 3. Symptomatic herpes zoster within 3 months prior to screening. 4. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, TB testing that includes: • a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours), and regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) OR • a positive (not indeterminate) QuantiFERON-TB Gold test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression. 5. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years. 6. Breast cancer within the past 10 years. 7. History of severe injection site reaction (i.e., required emergency care or hospitalization) following any prior injection, including reaction to vaccines. 8. History of clinically significant allergy or prior hypersensitivity, including those with a documented yeast allergy. 9. History of, or current concern for, a chronic immune deficiency disorder including, but not limited to: diabetes, sickle cell anemia, and malnutrition. 10. Hemoglobin levels below the normal range (as determined for gender).

11. Platelet count <130,000/mm^3.
12. Creatinine clearance (CrCL) <90 mL/min.
13. Alanine transaminase (ALT) >1.1x upper limit of normal (ULN).
14. Bilirubin >1.1xULN (isolated bilirubin >1.1xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
15. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
16. QTcF >450 msec.

PRIOR/CONCOMITANT THERAPY

17. Intended use of over-the-counter or prescription medication within 7 days prior to dosing. Specific medications listed in Section 7.7 may be allowed.
18. Live vaccine(s) within 1 month prior to screening, or plans to receive such vaccines during the study.
19. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.
20. Exposure to immune-modulating medications (including corticosteroids) within 30-days of Screening.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

21. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
22. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
23. Current enrolment or past participation within the last 30 days 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

24. Absolute CD4+ T-cell count <500 cells or CD4 percent (CD4%) outside of the normal range for the reference laboratory (32% to 64%).
25. Presence of Hepatitis B surface antigen (HBsAg) at screening.
26. Positive Hepatitis C antibody test result at screening.

NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

27. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention

NOTE: Test is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

28. Positive pre-study drug/alcohol screen.

29. Positive human immunodeficiency virus (HIV) antibody test

OTHER EXCLUSIONS
30. History of regular alcohol consumption within 6 months of the study defined as: an average weekly intake of >14 units. 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.
31. 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.
32. 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.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Participants should arrive fasted for the screening visit only and will be allowed to eat during the screening visit after blood draw for clinical chemistry has been completed.

6.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic and 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.

6.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 serious adverse events (SAEs).

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

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Table 13 Treatment Administration

Study Treatment Name:	GSK3732394	Placebo-0.9% w/v sodium chloride
Dosage formulation:	Solution for injection	Solution for injection
Unit dose strength(s)/Dosage level(s):	100 mg/mL	Volume to match active dose
Route of Administration	Subcutaneous injection	Subcutaneous injection
Dosing instructions:	Details can be found in Study Reference Manual	Details can be found in Study Reference Manual
Packaging and Labelling	Study Treatment will be provided in 1mL glass vials. Each will be labelled as required per country requirement.	Sourced by unit

7.2. 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 Safety and Dose Escalation Committee, based on safety, tolerability, and PK/PD data obtained from the prior dose level(s).

7.3. Method of Treatment Assignment

Subjects 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 validated internal software.

Each subject scheduled to receive study drug will receive a treatment allocation number when randomized. Study treatment will be administered at the study visits summarized in the Schedule of Assessments.

7.4. Blinding

This will be a double-blind study with participants and the site staff blinded, except for an unblinded pharmacist at the site who will prepare the blinded drug product. The blinded drug product will be administered by site staff not involved with assessments (to prevent unblinding due to the viscosity of active drug product vs. placebo).

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 SDEC 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.

Participants will be randomized in a 3:1 ratio to receive study treatment (GSK3732394 : PBO) within a cohort. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study.

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 treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or Sponsor policy.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- An unblinded pharmacist or designee will prepare blinded study treatment and provide to authorize study staff for administration.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of

unintentional occupational exposure notify the Study Sponsor Medical Monitor and/or Sponsor study contact.

7.6. Treatment Compliance

When participants are dosed at the site, they will receive study treatment 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 treatment 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 treatment.

GSK3732394 /PBO will be administered by subcutaneous injection to participants at the site. Administration will be documented in the source documents and reported in the CRF, including location of injection site(s).

7.7. Concomitant Therapy

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, an emergency situation in the opinion of the investigator or otherwise previously discussed with the Medical Monitor.

Permitted Medications are:

- Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study.
- In the event of irritation from ECG leads, up to 2.5% topical hydrocortisone may be used at the discretion of the investigator.
- Female subjects of childbearing potential are permitted to use the contraceptive methods outlined in Appendix 4, Section 12.4 and in Inclusion Criterion 5.

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that a participant is receiving at the time of enrolment or receives during the study must be recorded and reviewed with the Study Sponsor Medical Monitor. The following details should be included in the record:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

7.8. Treatment after the End of the Study

Since this is a study that includes healthy participants, no additional treatment from Sponsor, including GSK3732394, will be provided after the completion of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

A participant will 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.
- A Serious Adverse Event (SAE), regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3732394, in the opinion of the Investigator.
- A Grade 2-4 Acute Allergic reaction (DAIDS criteria), reasonably attributable to dosing with GSK3732394, in the opinion of the Investigator.
- A Grade 2-4 Hematologic AE (DAIDS criteria), reasonably attributable to dosing with GSK3732394, in the opinion of the Investigator.
- A Grade 3-4 Injection Site reaction (DAIDS criteria), reasonably attributable to dosing with GSK3732394, in the opinion of the Investigator.
- Grade 3-4 AE or Grade 3-4 clinically significant laboratory abnormality that is considered to be reasonably attributable to dosing with GSK3732394 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 (e.g., 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)

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 should complete an end-of-study/early termination evaluation per SOA.

8.1.1. Study Stopping Criteria

Safety parameters and the available pharmacokinetic parameters from the previous cohorts will be fully assessed by the SDEC 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 from the planned two-week interval to allow the collection of additional safety data if clinically indicated.

Dose escalation will be paused (until all of the cumulative safety data is reviewed by the Study Team and the VSLC) if the following number of participants, within an ongoing cohort of 6 active participants, develops these clinically significant AEs or changes in safety parameters (see also Section 8.1.1.1 through Section 8.1.1.5):

- One participant experiences an AE of Grade 4 intensity assessed as related to GSK3732394, as reported by the PI.
- One participant experiences a Serious Adverse Event (SAE) or death assessed as related to GSK3732394, as reported by the PI.
- One participant experiences a Grade 3 injection site reaction (per DAIDS criteria) related to dosing with GSK3732394.
- Two participants experience an AE of Grade 3 intensity assessed as related to GSK3732394, as reported by the PI.
- Two participants with confirmed QTcF ≥500 msec.
- ≥25% of participants (within a dosing cohort or across the entire study) receiving GSK3732394 have a ≥ Grade 2 intensity AE, lab abnormality (with the exception of asymptomatic changes in lipid panel), or injection site reaction (per DAIDS criteria)
- Or if the pattern of adverse events observed in a cohort are consistent across participants, poorly tolerable, and clinically significant.

In addition, the safety parameters listed below [i.e. dose limiting toxicities (DLTs)] will be monitored carefully and will be reviewed with the SDEC prior to all dose escalations. The intensity applied to all Adverse Events (AEs) will be determined using DAIDS criteria. The toxicity applied to all laboratory abnormalities will be determined using DAIDS criteria (See Appendix 6, Section 12.6). If clinically significant findings are observed in a considerable number of participants as outlined below, then dose escalation will be paused until all of the cumulative safety data is reviewed by the SDEC and shared with the ViiV (Sponsor) Safety and Labelling Committee (VSLC). The VSLC is comprised of senior representatives from various departments, including clinical development, toxicology, pharmacovigilance, epidemiology, and medical affairs.

8.1.1.1. Serious Allergic Reaction

If the following allergic reactions are observed in 1 or more participants within the ongoing cohort of 6 active participants, the dose escalation will be paused until all of the cumulative safety data is reviewed by the Study Team and the Sponsor VSLC:

- An acute hypersensitivity reaction adverse event (AE) (i.e, angioedema, bronchospasm, hives, hypotension, rash with concurrent fever/transaminitis/eosinophilia, etc.) of moderate to severe intensity (Grade 2-4 by DAIDS criteria) or,
- A delayed hypersensitivity reaction AE with systemic symptoms and/or end-organ effects (i.e., serum sickness, vasculitis, fever, arthralgia/myalgia, nephritis, etc.) of moderate to severe intensity (Grade 2-4 by DAIDS criteria).

NOTE: An event is defined as any observed change (or laboratory abnormality confirmed by a repeat blood sample) as outlined in Appendix 6, Section 12.6.

8.1.1.2. Hematological parameters:

If the following number of participants within the ongoing cohort of 6 active participants, develops clinically significant hematological changes (as outlined below), the dose escalation will be paused until all of the cumulative safety data is reviewed by the Study Team and the Sponsor VSLC:

- Two participants treated with GSK3732394 experience a confirmed reduction in baseline CD4 percent (CD4%) >25% at any time during the inpatient period or post-dosing outpatient follow-up; or
- Two participants treated with GSK3732394 experience a confirmed absolute CD4+ T-cell count that meets DAIDS Grade 1 toxicity (<400 cells/mm3) during the inpatient period or post-dosing outpatient follow-up; or
- One participant treated with GSK3732394 experiences a confirmed reduction in baseline CD4 percent (CD4%) >40% at any time during the inpatient period or post-dosing outpatient follow-up: or
- One participant treated with GSK3732394 experiences a confirmed absolute CD4+ T-cell count that meets DAIDS Grade 2 or greater toxicity (<300 cells/mm3).

8.1.1.3. Pharmacokinetic Dose Adjustment/Stopping Criteria for Part 1 (SAD) and Part 2 (MAD)

Pharmacokinetic stopping criteria for dose escalation across the study (Part 1 [SAD] and Part 2 [MAD]) will be applied if there is emerging evidence for a reduction in % CD4+ T-cells (>20% median maximum decline in CD4% among subjects receiving active drug) across any preceding dosing cohort. Under such circumstances, dose escalation will not progress beyond any single participant with exposures greater than NOAEL of 93.9 µg/mL for C_{max}.

As part of routine dose escalation, Bayesian probability that any individual at the next scheduled dosing level will exceed the C_{max} NOAEL exposure will be calculated. This probability, together with the safety, tolerability, PK and PD data of the previous cohorts, will be used to guide the selection of the next dose.

8.1.1.4. Liver Enzymes:

If the following clinical chemistry changes are observed in 1 or more participants within the ongoing cohort of 6 active participants, the dose escalation will be paused until all of the cumulative safety data is reviewed by the Study Team and VSLC**.**

- ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (>35% direct) – requires rapid evaluation, hepatology consult, and prompt notification of the Study Sponsor Medical Monitor
- ALT ≥ 3xULN

8.1.1.5. Vital Signs/ECGs:

If the following vital signs/ECG changes are observed in 1 or more participants within the ongoing cohort of 6 active participants, the dose escalation will be paused until all of the cumulative safety data is reviewed by the Study Team and the VSLC:

- Mean heart rate taken from the 12-lead ECG falls to less than or equal to 35 bpm or rises to greater than or equal to 120bpm on ECGs completed in triplicate over a <5min time period,

- Mean heart rate taken from the 12-lead ECG changes by more than 60bpm from pre-dose baseline of that dosing day on ECGs completed in triplicate over a <5min time period.
- Symptomatic or asymptomatic arrhythmia of any clinical significance as outlined below:
  - Sustained (5 or more beats for a duration of 30 seconds or more) or non-sustained (5 or more beats for a duration of less than 30 seconds) ventricular arrhythmias.
  - Sustained (5 or more beats for a duration of 30 seconds or more) supraventricular arrhythmias including atrial fibrillation and flutter
  - Complete bundle branch block
  - Pauses > 3 seconds
- Mean systolic blood pressure changes by more than 30mmHg and/or diastolic blood pressure changes by more than 20mmHg from pre-dose baseline upon blood pressure recordings completed in triplicate, at least 1min apart.

8.1.2. Individual Participant Stopping Criteria

8.1.2.1. Liver Chemistry Stopping Criteria

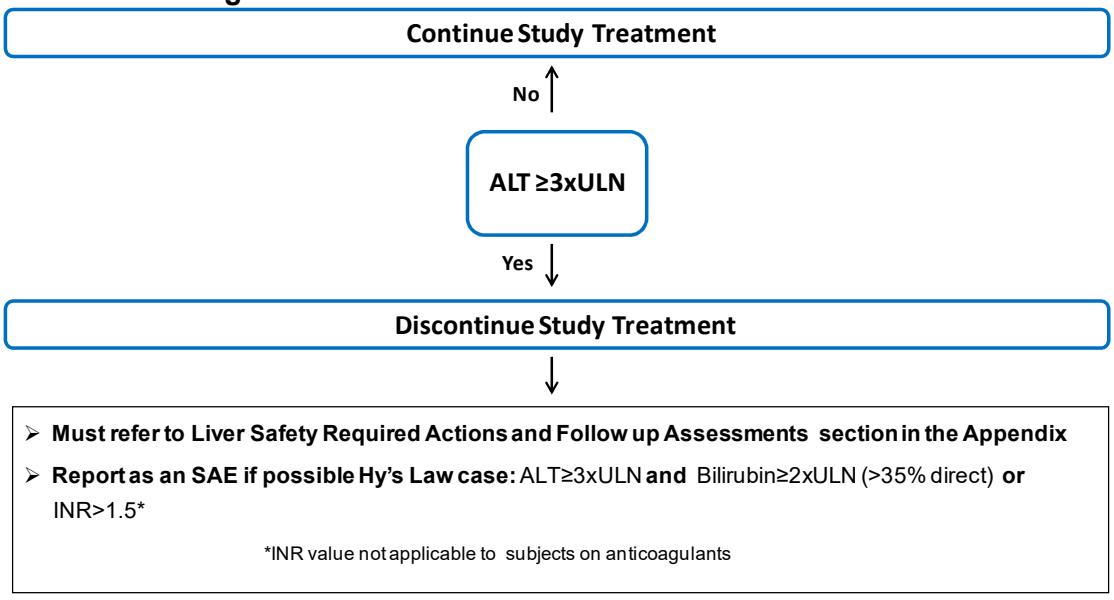
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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

- A participant meets one of the conditions outlined in Figure 3.
- 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 3 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.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 5, Section 12.5.

8.1.2.2. QTc Stopping Criteria

The Fridericia QT correction formula (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-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 treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.2.3. Other Individual Participant Safety-related Stopping criteria

A participant will be withdrawn if they develop a: Serious adverse event (SAE); Grade 2-4 allergic reaction; a Grade 2-4 abnormality in any hematology-related laboratory parameter; or a Grade 3-4 injection site reaction that is judged by the investigator to be plausibly related to the administration of active study medication, or any other AE that is deemed clinically significant by the investigator and is judged by the investigator to be related to the dosing of study product.

A participant may be withdrawn from the study if they present with any dose limiting toxicity as defined in Section 8.1.1. If dose limiting toxicity (DLT) is observed in an individual, and dose-interruption criteria are not otherwise met (per Section 8.1.1), the Investigator or designee may use their medical judgment and stop any further dosing and must immediately inform the Sponsor medical monitor or designee. Together, the PI and Medical Monitor will decide further management of the individual participant. The SDEC may be convened at any time in request of a comprehensive review of the data to help in decision-making around the management of an individual participant or subsequent dosing.

8.1.3. Temporary Discontinuation

Temporary discontinuation in this study is not allowed.

8.1.4. Rechallenge

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

8.2. 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.

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.

Refer to the Section 2 for data to be collected at the time of study discontinuation and/follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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 should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Section 2.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Section 2, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, 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.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL in a 56-day period.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples

9.1. Efficacy Assessments

Not applicable.

9.2. Safety Assessments

Planned time points for all safety assessments are provided in the Section 2.

9.2.1. Physical Examinations

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

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

Injection sites will be examined as part of both complete and targeted physical exams.

9.2.2. 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 single oral temperature, pulse rate, respiratory rate, and blood pressure measurements. If abnormalities in pulse or blood pressure are noted, repeat recordings should be measured in triplicate, at least 1 minute apart. The average of the 3 readings will be recorded on the CRF.

9.2.3. Electrocardiograms

The frequency of ECGs 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, 2010)

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

If any abnormalities in ECG interval are noted (including prolongation of the QT interval), ECGs should be repeated in triplicate with recordings over a 5min time period. Refer to Section 8.1.2.2 QTc Stopping Criteria for QTc withdrawal criteria and additional QTc readings that may be necessary.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

At least one of these ECGs will be available and reviewed by the PI on site to evaluate for QT prolongation. Additional ECGs beyond those described in the SoA table can be obtained by the PI should they suspect a prolongation in the QT interval.

9.2.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and Section 2 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 2 days after the last dose of study treatment 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 will 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 Section 2.

9.2.5. T cell Assessments

A battery of tests to determine the effects of GSK3732394 on T cells will be collected as noted in the SoA, including:

- CD4/CD8/CD3 absolute number and percent (as part of hematology panel, see Section 12.2)
- CD4 median fluorescence intensity (MFI) (as part of pharmacodynamic assessment)
- Activated CD4 T-cells (CD4+/CD25+) (as part of pharmacodynamic assessment)

9.3. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3, Section 12.3.

As described Appendix 3, Section 12.3 and Appendix 6, Section 12.6, intensity of AEs (and lab abnormalities) will be graded using the DAIDS Grading table. While the study population will consist of HIV-1 seronegative healthy adults, 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 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 treatment or the study, or that caused the participant to discontinue the study treatment and/or study (see Section 8).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2). 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 treatment until the follow-up visit at the time points specified in the SoA (Section 2).

- Medical occurrences that begin before the start of study treatment 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 should this exceed 24 hours, as indicated in Appendix 3, Section 12.3.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.

9.3.2. 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, Section 12.3.

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.

9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3, Section 12.3.

9.3.4. 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 treatment 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 treatment 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.

9.3.5. 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 40 days after last dose of study medication.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4, Section 12.4.3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.4. Treatment of Overdose

For this study, any dose of GSK3732394 greater than the specified dose for that cohort will be considered an 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 GSK3732394 can no longer be detected systemically (approximately 11 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 SDEC.

9.5. Pharmacokinetics

Serum samples of approximately 1 mL (from 2 ml of blood) will be collected for measurement of serum concentrations of GSK3732394 and GSK3732394-related material identification as specified in the SoA. A maximum of 5 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 and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

Samples will be used to evaluate the PK of GSK3732394. Samples collected for analyses of GSK3732394 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Once the serum has been analyzed for GSK3732394, any remaining serum may be analyzed for other GSK3732394-related materials and the results reported under a separate protocol.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.6. Pharmacodynamics

Venous blood samples of approximately 2 mL will be collected for measurement of CD4+ T cell receptor occupancy, CD4+ T cell MFI, and activated T cells (CD25+) at time points specified in the SoA. The actual date and time (24-hour clock time) of each sample will be recorded. Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

9.7. Non-Pharmacokinetic Sample Collection

Urine samples will be collected from each subject prior to dosing (the pre-dose sample can be collected up to 48 hours before dosing) and during the timepoints noted in the SoA. Urine collection will be only during the highest dose cohort in both Part 1 (SAD) and Part 2 (MAD) for 24 hours after the last dose. Processing, storage and shipping procedures are provided in the SRM.

Urine will be analysed for possible GSK3732394-related metabolites. If identified, results will be reported under a separate protocol.

9.8. Biomarkers

Collection of serum samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from participants in this study are specified in the SoA (see Section 2).

Other samples may be used for research to develop methods, assays, related to the mechanism of action of the study treatment.

9.8.1. Immunogenicity Assessments - Anti-GSK3732394 antibodies

Serum samples for testing for antibodies against GSK3732394 will be collected at the time points indicated in the SOA. The actual date and time of each blood sample collection will be recorded. Processing, storage and shipping procedures are provided in the SRM.

The presence of anti-GSK3732394 antibodies will be determined in serum samples using a validated bioanalytical method, which includes a screening assay, confirmation assay and titer analysis. Positive samples may be further characterized with additional assays to determine the specificity of the anti-GSK3732394 antibodies to the different domains of GSK3732394.

9.8.2. Immunogenicity Assessments - Immune activation

Serum samples for biomarkers of immune activation (cytokines including but not limited to IFNγ, IL6, IL8, TNFα, and IL2) will be collected at baseline and after dosing only if clinically indicated (i.e., participant displays signs or symptoms of immune activation). Processing, storage and shipping procedures are provided in the SRM.

9.9. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

No formal statistical hypotheses are to be tested. Sample size is based on feasibility. No formal calculation of power or sample size (i.e., sample size sensitivity or robustness) will be performed. A sample size of approximately 8 participants (6 active:2 placebo) in each SAD and MAD cohort should be sufficient to provide useful estimates of inter-participant variability for GSK3732394, PK and PD parameters and initial safety assessments. Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of observing AEs. With 6 participants receiving each dose of active study treatment, if the true adverse outcome rate is 5%, the chance of seeing at least 1 adverse outcome at a given dose is 26%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least 1 adverse outcome at a given dose is 74%.

Sample size re-estimation is not planned.

Data will be reviewed by the Safety and Dose Escalation Committee (SDEC) prior to each dose escalation; no other interim analysis is planned.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who passed screening and entered the study. Included are: Randomized Participants. Note: Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population, as they did not enter the study.
Safety	All participants who received at least 1 dose of study treatment. Participants will be analyzed according to the treatment they received.
Pharmacokinetic (PK)	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).

10.3. Statistical Analyses

10.3.1. 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
Adverse events (AEs)	The proportion of participants reporting AEs will be tabulated by treatment and by cohort. AEs will also be tabulated by severity and relationship. AEs will be tabulated using 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.
Clinical laboratory	Laboratory results will be included in the reporting of this study for hematology, clinical chemistry, and urinalysis. Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within the normal range) and high (above the upper limit). Summary statistics for change from baseline will also be tabulated.
Vital signs assessments	The following Vital Signs measurements will be tabulated: supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature. Summary statistics for change from baseline will also be tabulated.

10.3.2. Pharmacokinetic Analyses

All pharmacokinetic analyses will be performed on the Pharmacokinetic Population. For the PK endpoints in this study, no formal hypotheses will be tested.

Endpoint	Statistical Analysis Methods
Secondary	Plasma GSK3732394, concentration-time data will be analysed by non-compartmental methods using WinNonlin Professional 5.2 or higher, Phoenix (Pharsight Corporation) or comparable software. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: <u>Part 1 (single dose)</u> Area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$ and $AUC_{(0\ \infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), t_{lag}, C_{last}, t_{las}, t_{trough} plasma drug concentration (C_{trough}) and terminal half-life ($t_{1/2}$,) CL/F <u>Part 2 (Repeated weekly dosing):</u> First week: $AUC_{(0-t)}$, $AUC_{(0-tau)}$, $AUC_{(0\ \infty)}$, C_{max}, t_{max}, t_{lag} Last week: $AUC_{(0-\tau)}$, C_{max}, t_{max}, C_{trough}, $t_{1/2}$, CL/F <u>Part 1 (single dose)</u> Dose proportionality will be assessed by visual inspection of dose normalised $AUC_{(0-\infty)}$ [or if not available $AUC_{(0-t)}$] and C_{max} values versus dose. Analysis of these log_e-transformed parameters may be carried out, using the power model. <u>Part 2:</u> The extent of accumulation after repeat dosing, the observed accumulation ratio, may be determined. Accumulation indices for PK parameters assessed across first and last doses of multiple dosing, as data allow: $RAUC_{(0-tau)}$, RC_{max}, RC_{trough}. For repeat dosing, $AUC_{(0-tau)}$, C_{max}, C_{trough} will be analyzed versus dose for the dose-proportionality. Further details will be included in the RAP

10.3.3. Interim Analyses

There will be no formal interim analysis; however, all preliminary safety, tolerability, and available PK/PD data will be reviewed internally prior to each dose escalation. Dose escalation can only occur after the Safety and Dose Escalation Committee (SDEC) has found that the safety, PK/PD profiles are supportive to proceed with the evaluation of the next higher dose level.

PK/RO modelling will be performed to determine the parameters E_{max}, EC50 and Hill-coefficient, as data permits.

Beginning with the second dose in Part 1 and each subsequent dose throughout the study, the Bayesian probability of any individual participant exceeding the C_{max} NOAEL exposure of 93.9 µg/mL at that dose will be calculated, using the accumulated PK data of participants receiving GSK3732394 among the previous cohorts. Observations on placebo will be excluded. This probability, together with safety and tolerability data of the preceding cohorts, will be used to help selection of the next dose. The Bayesian probability of exceeding the C_{max} threshold can be calculated for additional potential doses to aid in dose selection if necessary.

The Bayesian probability will be based on Whitehead's model shown below [Whitehead, 2001].

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

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. εi is the random error of the i-th participant.

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

Bayesian model Operating Characteristics (OC)

Here we explore the operating characteristics of the planned highest expected dose of the MAD portion of the study of 600mg. We are interested in the probability that no participant will exceed C_{max} NOAEL of 93.9 µg/mL. Additionally, we are interested in the predicted maximum exposure among the 6 participants receiving the 600mg dose. We simulated data for 1000 trials using Whitehead's model, based on different C_{max} variability (CV%) assumptions ranging from 30% to 60% (assuming dose proportionality: θ_2=1) and θ_1=$\log_{(0.06355)}$. The value of θ_1 values is based on the predicted human exposure using preclinical data. Each simulation contains data for 2 cohorts of 6 participants each on active doses of 130mg and 400mg.

For each simulated trial the MCMC procedure was used assuming Whitehead's model for log(C_{max}) response (without assuming dose proportionality) with noninformative priors on the model parameters. Ten thousand (10,000) iterations were used and, for each iteration simulated $\log_{(Cmax)}$ value, each of six participants on the planned top dose of 600mg using the posterior distribution of $\log_{(Cmax)}$ obtained from the MCMC procedure. The proportion of iterations with any of the six new observations exceeding $\log_{(93.9)}$ is the Bayesian probability (using data from the preceding doses) of any participant on the 600mg dose exceeding the NOAEL exposure of 93.9 µg/mL.

Additionally, we calculated the maximum C_{max} exposure among the 6 participants (by transforming the $\log_{(Cmax)}$value) and averaged the max value across all iterations. This is the predicted maximum exposure among the 6 participants on the 600mg dose.

Table 14 shows the predicted value of the maximum exposure among the 6 participants on the 600mg dose, averaged across all 1000 simulations, depending on CV%. Also shown in Table 6 is the percentage of 1000 simulated trials with Bayesian probability of any individual exceeding the C_{max} NOAEL below the thresholds of 40%, 50%, and 60%.

Table 14 Predicted Maximum C_{max} Value of 6 Participants on 600mg Dose and Percentage of Trials with Bayesian Probability Less Than the Threshold (40%, 50%, or 60%)

CV%	C_{max} (µg/mL)	Probability Threshold		
		40%	50%	60%
30	61.2	99.0%	99.9%	99.9%
40	72.8	88.9%	94.9%	98.6%
50	87.5	72.8%	84.3%	91.6%
60	106.0	59.1%	71.5%	82.7%

Based on Table 14, when the C_{max} variability is low-moderate, the predicted maximum C_{max} exposure among the 6 participants on the 600mg dose is below the NOAEL of 93.9 µg/mL and the majority of simulated trials had Bayesian probability of any individual exceeding the C_{max} NOAEL below the thresholds of 40%, 50%, and 60%.

10.3.4 Final Analyses

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

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

Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-participant CV (%CVb) for continuous variables, whereas n and percent will be used as summary statistics for categorical variables.

11. REFERENCES

Bussiere JL. "Animal models as indicators of immunogenicity of therapeutic proteins in humans." *Dev Biol,* 01-Jan-2003, 112:135-9.

Darpo B. The thorough QT/QTc study 4 years after the implementation of the ICH E14 guidance. *British Journal of Pharmacology.* 2010;159(1):49-57. doi:10.1111/j.1476-5381.2009.00487.

GlaxoSmithKline Document Number 2017N344293_00. Evaluation of the antiviral efficacy of GSK3732394 (BMS-986197) in a humanized mouse model of HIV-1 infection. Effective Date December 2017.

GlaxoSmithKline Document Number 2018N358742_00. GSK3732394 Investigator's Brochure, Version 1.0. 10-April-2019

GlaxoSmithKline Document Number 2018N365256_01. Clinical Pharmacology Review; Chakradhar Lagishetty (GSK) and Mark Baker (ViiV Healthcare), 14-MAR-2019.

Whitehead J, Patterson S, Webber D, Francis S, Zhou Y, Easy-to-implement Bayesian methods for dose-escalation studies in healthy participants, *Biostatistics*. 2001;2(1):47-61.

12. APPENDICES

12.1. Appendix 1: Study Governance Considerations

12.1.1. 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

12.1.2. 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.

12.1.3. 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.

12.1.4. 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.

12.1.5. Committees Structure

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

12.1.6. 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.

12.1.7. 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 subjects, 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.

12.1.8. 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.
- 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 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.1.9. 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.

12.1.10. 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

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 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.
- Pregnancy Testing:
    - Refer to Section 6.1 Inclusion Criteria for screening pregnancy criteria.
    - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
    - 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 subject's participation in the study.

Table 15 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Lymphocyte Phenotype Absolute number and Percent of: CD3+ CD4+ CD8+
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Amylase
	Lipase			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other 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)[2] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] • Creatinine clearance (CrCL) for GFR estimation • 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 8.1 and Appendix 5 (Section 12.5). 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).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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.

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

12.3.1. 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 treatment, whether or not considered related to the study treatment.
- 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 treatment.

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 treatment 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 treatment 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 (eg, 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.

12.3.2. 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 (e.g., 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 should 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.

12.3.3. Recording 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 treatment 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 treatment 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 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 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 GSK within 24 hours of receipt of the information.

12.3.4. Reporting of SAE to Study Sponsor

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to 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.

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

12.4.1. 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 enrollment.

12.4.2. Contraception Guidance

12.4.2.1. Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 16 when having penile-vaginal intercourse with a woman of childbearing potential

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for at least 30 days from last dosing.

In addition, male participants must refrain from donating sperm for duration of study and for at least 100 days, or 5 half-lives plus 90-days for sperm turnover, whichever is longer, from last dosing.

12.4.2.2. Female participants

Non-pregnant female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 16.

Table 16 Highly Effective Contraceptive Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE: To be used during the treatment period and for at least 28 days prior to first dose, and 40 days after, the last dose of study treatment.
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate <1% / 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 <1% / 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. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test conducted at Screening
- Additional pregnancy testing will be performed in WOCBP on a monthly basis, including at the end-of-study evaluation
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed

12.4.3. Collection of Pregnancy Information

12.4.3.1. 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 GSK3732394.
- 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.

12.4.3.2. 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 will be reported as an AE or SAE.
- A spontaneous abortion 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 4 (Section 12.4.3). 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.

12.5. 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 subject until liver chemistries resolve, stabilise, or return to within pre-dose (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 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within pre-dose • A specialist or hepatology consultation is recommended **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 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within pre-dose	• 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 (PK) 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 **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 threshold value stated will not apply to subjects 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 subjects 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 subject'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.

12.6. Appendix 6: Division Of AIDS (DAIDS) Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 2.1 July 2017

See https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2

12.7. Appendix 7: Abbreviations and Trademarks

ADA	Antidrug antibody
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ARV	Anti-retroviral
$AUC_{(0-t)}$	Area under the plasma concentration time curve from zero to t
$AUC_{(0-\tau)}$	Area under the curve (Area under the concentration-time curve at steady state within the dosing interval)
$AUC_{(0-24)}$	Area under the concentration time curve from zero to 24
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
$AUC_{(0-tlast)}$	Area under the concentration-time curve from zero to time of last sample taken
BMI	Body mass index
BMS	Bristol-Myers Squibb
bpm	Beats per minute
CD	Cluster of differentiation
CDR	Complementarity determining region
CI	Confidence interval
CIB	Clinical Investigator's Brochure
CL/F	Apparent clearance
Clast	Last observable concentration
C_{max}	Maximum observed concentration
C_{τ}	Trough concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
CV%	Coefficient of variation
DAIDS	Division of AIDS
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First-time-in-human
GCSP	Global Clinical Safety and Pharmacovigilance
GCP	Good Clinical Practices
GI	Gastrointestinal
HAART	Highly Active Anti-retroviral Therapy
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
hCD	Human Cluster of Differentiation
HIV-1	Human immunodeficiency virus-1
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal Replacement Therapy
ICF	Informed consent form
IEC	Independent Ethics Committee
IL	Interleukin
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IRB	Institutional Review Board
MAD	Multiple ascending dose
MFI	Median Fluorescence Intensity
MOA	Mechanisms of action
NOAEL	No observed adverse effect level

NQ	Non-quantifiable
OC	Operating Characteristics
PBO	Placebo
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
$RAUC_{(0-\tau)}$	$AUC_{(0-\tau)}$ on week 4 to $AUC_{(0-\tau)}$ on week 1
RCmax	Cmax on week 4 to Cmax on week 1
RC_{τ}	C_{τ} on week 4 to C_{τ} on week 1
RAP	Reporting and Analysis Plan
RO	Receptor occupancy
SAD	Single ascending dose
SAE	Serious Adverse Event
SD	Standard deviation
SDEC	Safety and Dose Escalation Committee
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Apparent terminal phase half-life
tlag	Lag time
T_{last}	Time of last observable concentration
t_{max}	Time of occurrence of Cmax
TMDD	Target mediated drug disposition
ULN	Upper limit of normal
VSLC	ViiV Safety and Labelling Committee
WOCBP	Women of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
MedDRA
Phoenix
QuantiFERON
WinNonlin

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment (Amendment 03) Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Protocol Amendment 02 Changes – Effective 02-JUL-2019
Overall Rationale for the Amendment: This amendment results from a consensus between the Sponsor and the Study Site, that a confirmation of CD4+ T-cell count and CD4 percent values in healthy individuals with values within the normal range at screening, to be unnecessary. The removal of this confirmatory test is not determined to have effect on the evaluation of participant safety by the Sponsor or Study Site.

Section # and Name	Description of Change	Brief Rationale
Section 3.3.1 – Risk Assessment	Removed the word "confirmed" from 2nd bullet of the Mitigation Strategy for "CD4+ cell reduction / Impairment in Immune Function"	Unnecessary testing for participants.
Section 6.2 – Exclusion Criteria, Criterion 24	Removed "(to be confirmed at baseline, e.g., Day -1)" from this criterion.	Unnecessary testing for participants.

Protocol Amendment 01 Changes – Effective 06-JUN-2019

Overall Rationale for the Amendment: This amendment results from FDA "Study May Proceed" letter for IND Opening (Number 131394, Reference ID 4441322) dated 31-MAY-2019. FDA requested 9 clinical changes to the protocol, listed below.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 – Overall Design, Part 1, Paragraph 3	Revised to include sentinel participants for every SAD cohort rather than only the first three SAD cohorts.	FDA requested change, Clinical item #5
Section 5.2 – Number of Participants, Paragraph 3	Revised to clarify that participants will not be replaced if they discontinue study due to reasons of safety.	FDA requested change, Clinical item #4
Section 6.2, Exclusion Criterion #4	Revised for clarity. Prior text could be understood to mean that a volunteer with a positive PPD but negative CXR (latent TB) would be eligible. Revised to clarify exclusion for either a positive PPD or a positive QuantiFERON gold.	FDA requested change, Clinical item #6
Section 6.2, Exclusion Criterion #8	Revised to also exclude volunteers who have documented yeast allergies.	FDA requested change, Clinical item #1
Section 6.2, Exclusion Criteria #10 and #11 (new criteria)	Revised laboratory abnormality exclusion criteria.	FDA requested change, Clinical items #2c and #2d.
Section 6.2, Exclusion Criterion #12 (new criterion)	Requested renal exclusion criterion to limit enrolment to volunteers with normal renal function.	FDA requested change, Clinical item #3
Section 6.2, Exclusion Criterion #13	Revised laboratory abnormality exclusion criteria.	FDA requested change, Clinical item #2a.
Section 6.2, Exclusion Criterion #13	Revised laboratory abnormality exclusion criteria.	FDA requested change, Clinical item #2b.
Section 8.1, Discontinuation of Study Treatment, new bullet	Revised to include: "Grade 3-4 AE or Grade 3-4 clinically significant laboratory abnormality that is considered to be reasonably attributable to dosing with GSK3732394 in the opinion of the investigator."	FDA requested change, Clinical item #7
Section 8.1.1, Study Stopping Criteria	Consolidated "Other Study Stopping Criteria" previously listed in Section 8.1.1.6 into Section 8.1.1.	FDA requested change, Clinical item #8
Appendix 2, Table 15	Added Amylase and Lipase under Clinical Chemistry and added creatinine clearance under Other Screening Tests	FDA requested change, Clinical items #3 and #9.
Not applicable	Other administrative changes for items such as typographical errors or grammatical corrections.	Clarity