Protocol

Study ID: 207959

Official Title of Study: A Phase 2a Multicentre, Randomized, Open-Label, Two-Part Adaptive Design Study to Evaluate the Antiviral Effect, Safety and Tolerability of GSK3810109A, an HIV-1 Specific Broadly Neutralizing Human Monoclonal Antibody in Antiretroviral-naïve HIV-1-Infected Adults

NCT Number-NCT04871113

Approval Date of Document: 26-Jul-2021

TITLE PAGE

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Protocol Number: 207959/ Amendment 04

Compound Number: GSK3810109A

Study Phase: Phase 2a

Short Title: GSK3810109A Proof Of Concept in Viremic HIV-1 Infected Adults

BANNER: Broadly-neutralizing Antibody N6LS in ART-Naives to Evaluate virologic Response

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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 can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s):

US IND: 148241

Approval Date: XX-XXX-2021

SPONSOR SIGNATORY:

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 4	XX-XXX-2021	TMF-13894674
Amendment 3	11-MAR-2021	TMF-11879657
Amendment 2	05-NOV-2020	2018N378492_02
Amendment 1	01-SEP-2020	2018N378492_01
Original Protocol	14-JUL-2020	2018N378492_00

Amendment 4: XX-XXX-2021

Overall Rationale for Amendment 4: Inclusion criteria have been edited for clarity and to reduce the CD4+ eligibility threshold. Group 1 (high dose) sample size required for the interim analysis has been updated from 10 to approximately 10 evaluable participants to clarify that the interim analysis may proceed with a lower number, as supported by the sample size sensitivity analysis included in the protocol.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	207959 is designed as an open-label study; an open label trial design affords the availability of real time safety data following antibody infusions. Based upon the small sample size (approximately 10 participants for all Groups in Part 1 and Part 2) and the open-label trial design, safety and tolerability will be assessed in-stream (via a Safety Review Team) as well as at defined analysis timepoints (via the Safety and Dose Evaluation Committee). Enrollment in Part 1 will continue until approximately 10 evaluable participants are confirmed in Group 1.	Group 1 sample size updated to "approximately 10" for consistency with other dosing groups.
5.2 Inclusion Criteria	Participants must have documented HIV-1 infection at the Screening Visit: • Plasma HIV-1 RNA ≥5000 c/mL. NOTE: A single repeat test is allowed to determine eligibility. An HIV-1 RNA result ≥5000 c/mL will serve as confirmation of HIV-1 infection. Screening CD4+ T-cell count ≥ 250 cells/mm^3: NOTE: A single repeat test is allowed to determine eligibility.	Changes made to clarify eligibility criteria, and change the entry threshold for screening CD4+ cell count.

Section # and Name	Description of Change	Brief Rationale
8.0 Study Assessments and Procedures	Part 1 of the study will evaluate two doses of GSK3810109A administered by IV infusion on Day 1 in the 2 groups. Enrollment in Part 1 will continue until approximately 10 evaluable participants are confirmed in Group 1 to support the Go / No Go criteria (see Section 4.4 and Section 9.5). Participants will be randomized equally (1:1) between Group 1 and 2.	Group 1 sample size updated to "approximately 10" for consistency with other dosing groups.
9.2 Sample Size Determination	The sample size of approximately 10 evaluable participants for Group 1 was chosen to allow for an accurate estimate of the primary treatment effect of the highest dose. A sample size of approximately 10 for the remaining groups was chosen primarily based on feasibility in order to explore approximately 4 additional groups at varying dose concentrations and modes of delivery (IV and subcutaneous). The required sample size of approximately 10 for Group 1 is to be able to account for the possibility of some participants being non-sensitive to GSK3810109A, and to accurately estimate the primary treatment effect among the sensitive-only subgroup.	Group 1 sample size updated to "approximately 10" for consistency with other dosing groups.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2a Multicentre, Randomized, Open-Label, Two-Part Adaptive Design Study to Evaluate the Antiviral Effect, Safety and Tolerability of GSK3810109A, an HIV-1 Specific Broadly Neutralizing Human Monoclonal Antibody in Antiretroviral-naïve HIV-1-Infected Adults

Short Title: GSK3810109A Proof Of Concept in Viremic HIV-1 Infected Adults

Rationale: This Phase 2a proof of concept (PoC) trial will be the first study of GSK3810109A (N6LS) in HIV-infected participants and will evaluate the efficacy, safety, tolerability, and pharmacokinetics of the broadly neutralizing HIV antibody GSK3810109A in treatment naïve viremic adults after a single dose administered as infusion or SC injection. Data from this study will be utilized to select doses and routes of administration for further studies of GSK3810109A in combination with other ART in Phase 2b and beyond.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the antiviral activity following a single dose of GSK3810109A in treatment-naïve HIV-1 infected participants	Plasma HIV-1 RNA maximum change from Baseline during the monotherapy phase
• To assess safety parameters following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Adverse events, Grade 2-4 ALT/ AST, treatment-emergent ECG abnormalities and Grade 2-4 injection site reactions
Secondary	
• To characterize the pharmacokinetics of GSK3810109A in treatment-naïve HIV-1 infected participants following a single IV or SC administration	GSK3810109A PK parameters following single dose administration e.g.: AUC (0-t), Cmax, Tmax, Ct
• To explore the potency of GSK3810109A	Relationship between GSK3810109A exposure and change in plasma HIV-1 RNA over time.
• To assess the immunologic changes following a single IV or SC dose of GSK3810109A	Absolute values and change in T cell counts from baseline over time
• To assess whether anti-drug antibodies develop following a single dose of GSK3810109A	Incidence of and titre in serum of anti GSK3810109A antibodies over time

Objectives	Endpoints
Safety	
• Safety and tolerability of GSK3810109A following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Clinical laboratory parameters, ECGs, vital signs, and injection site reactions over time.

Overall Design: Protocol 207959 is a two-part, randomized, open label adaptive design study to characterize the antiviral activity, safety/tolerability, PK and PK/Pharmacodynamics (PD, HIV-1 RNA decline) of GSK3810109A administered both intravenously (IV) and subcutaneously (SC) in HIV-1 infected, treatment-naïve adults. The study design includes a screening phase, a randomized monotherapy phase and a standard of care follow-up phase. The two parts of the randomized phase will each include a single dose monotherapy evaluation period after which all participants will enter a long-term follow-up period during which participants will initiate an appropriate integrase-based standard of care treatment regimen.

Disclosure Statement: This is an open-label, sequential, treatment, two-part, parallel group treatment study with up to 6 arms.

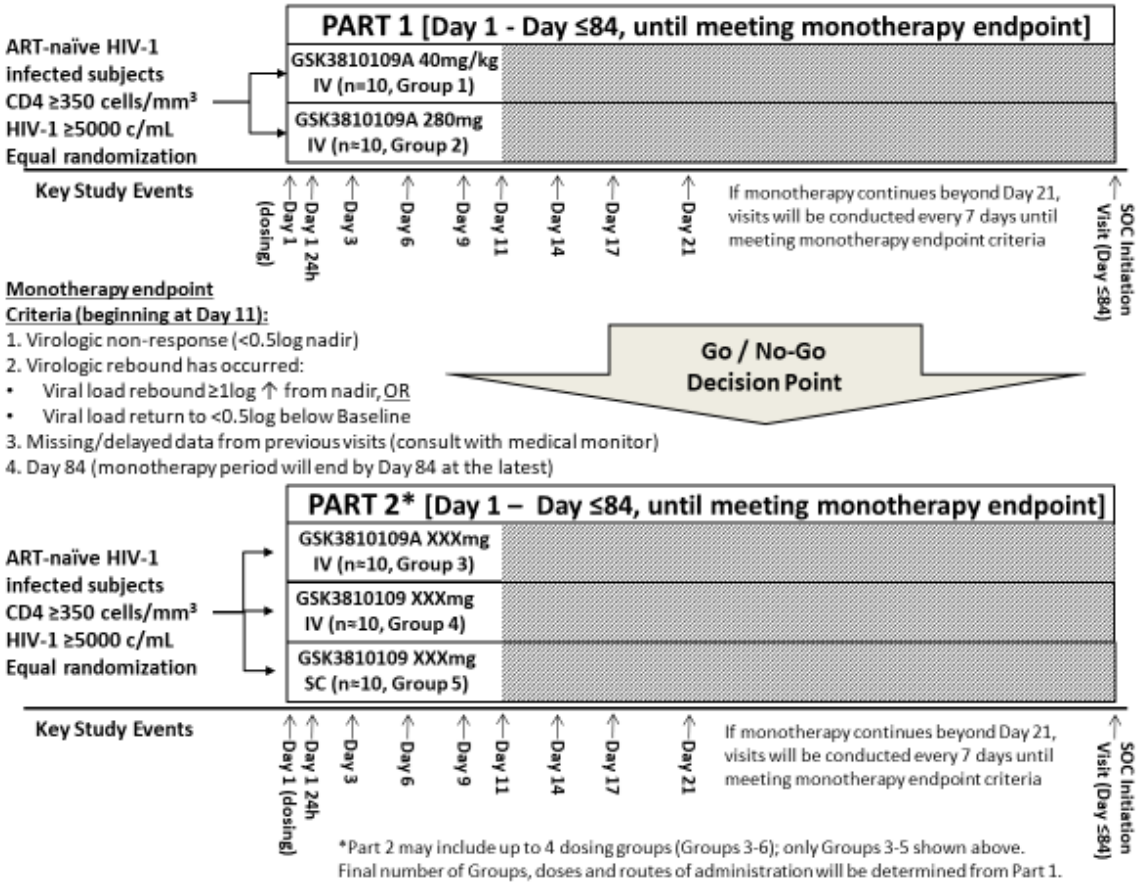
Number of Participants: Approximately 85 participants will be screened to achieve up to 60 randomly assigned to study intervention and 50 evaluable participants for an estimated total of 10 evaluable participants per intervention group.

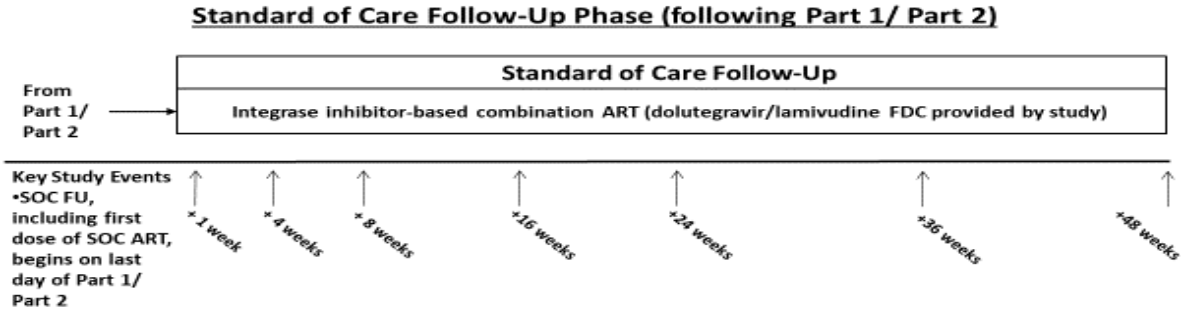
Intervention Groups and Duration: The study is designed in two parts, with Part 1 comprised of two parallel, randomized IV dosing groups followed by an interim review where pre-defined Go/No Go criteria will be assessed. Part 2 will follow a positive review of the Go/No Go criteria and will be comprised of up to 4 parallel, randomized dosing groups, with the potential for both IV and SC dosing.

Both Part 1 and Part 2 will employ a response-guided approach to the monotherapy period followed by a 48-week standard of care follow-up period. The duration of the study is up to 28 days for screening, up to 84 days for the monotherapy period and 48 weeks for the SOC follow-up period for a total maximum duration of approximately 15 months.

Data Monitoring Committee: A Safety and Dose Evaluation Committee (SDEC) will be used to ensure data integrity in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions for this study. The Committee will review emerging data and make recommendations per the Go/No Go criteria included in this protocol, recommend study changes, including dose for Part 2, and review safety parameters during the course of the study. A No Go decision by the SDEC will apply to all subsequent dosing groups. The details and composition of the Safety and Dose Evaluation Committee will be included in a Charter, to be completed prior to commencement of enrollment in study 207959.

1.2. Schema





1.3. Schedule of Activities (SoA)

Please note the following information regarding this adaptive study design:

- The timing and number of planned study assessments, including HIV-1 RNA, safety, pharmacokinetic, pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data to adequately characterize the viral load decline and return to baseline value). Please see Table 3 for allowable visit windows for study visits noted within the SOA.

- Any changes in the timing or addition/deletion of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by relevant study team members and then archived in the sponsor and site study files but will not constitute a protocol amendment.

- The Regulatory Agencies and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the Regulatory Agencies and the EC before implementation.

1.3.1. Screening Schedule of Activities

Procedure	Screening	Notes: Participants should be randomized (Randomization to occur on Day 1) within 28 days from the Screening Visit. Screening may be extended up to one additional week if lab results are pending (randomization or screen failure must occur within 35 days following the Screening Visit). See also Section 8 for descriptions of assessments
Clinical Assessments		
Written Informed Consent	X	
Eligibility Verification (Inclusion and Exclusion Criteria)	X	
Demography	X	Sex at birth and current gender will be collected.
Medical/Medication History	X	HIV risk factors may be collected at a later study visit
Symptom Directed Physical Exam and Medical Assessment	X	
Weight, Height and BMI	X	Participants should remove shoes and weigh on the same scale at each visit if possible.
Vital signs, including temperature	X	blood pressure, heart rate and body temperature
12-lead ECG	X	Triplicate ECGs as per Section 8.2.4
Prior PEP/PREP Therapy	X	See Inclusion Criterion #4
CDC Classification for HIV-1 Infection	X	See Appendix 8: CDC Classification for HIV-1 Infection (2014)
HIV Associated Conditions	X	
Laboratory Assessments		
Quantitative plasma HIV-1 RNA	X	
HIV Genotype/ Phenotype (RT/PRO/INI)	X	
Lymphocyte Subset	X	CD4/CD8 Absolute values and %
Clinical Chemistry	X	
Hematology	X	
Fasting Labs	X	Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides
CCI [redacted]		
Hepatitis B and C Screening	X	
Pregnancy test (POCBP only)	S	S=serum testing, See Section 8.3.5
Rapid Plasma Reagin (RPR)	X	
Urinalysis	X	
PT/PTT/INR	X	
CCI [redacted]		

Procedure	**Screening**	**Notes:** Participants should be randomized (Randomization to occur on Day 1) within 28 days from the Screening Visit. Screening may be extended up to one additional week if lab results are pending (randomization or screen failure must occur within 35 days following the Screening Visit). See also Section 8 for descriptions of assessments
COVID-19 testing	X	
Other Assessments		
SAE review	X	

1.3.2. Monotherapy Phase Schedule of Activities

Procedure	Monotherapy Phase (Part 1/ Part 2)[1]													ED	Follow-up[4]	Notes See also Section 8 for descriptions of assessments E.D = early discontinuation/withdrawal
	Day 1				Day 3 - Day 21[2]							Every 7 days (up to Day 84)[2]	SOC Initiation[3]			
	Pre-Dose	Infusion/ Injection	In clinic follow-up[5]	24h	3	6	9	11	14	17	21					
Clinical Assessments																
Entry Criteria	X															
Randomization	X															Day 1 prior to dosing
Vital signs	X	X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	Blood pressure, heart rate and body temperature will be collected at all timepoints; SpO2 and respiratory rate will be monitored for 4 hours following dosing. Body weight and height should be recorded at Day 1 Pre-Dose and used for dose calculation, if required. Body weight and height is not required at other visits during the Monotherapy Phase.
12-lead ECG	X		X[8]										X	X		Triplicate ECGs as per Section 8.2.4
CDC Classification	X															
HIV Associated Conditions													X	X		
Concomitant Medications	X	X[7]	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	
IP (GSK3810109A) Administration		X														Infusion should be performed over approximately 30 minutes; for SC injections, please refer to Section 6.4.
AE/SAE Review	X	X[7]	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Monotherapy Phase (Part 1/ Part 2)[1]													ED	Follow-up[4]	Notes See also Section 8 for descriptions of assessments E.D = early discontinuation/withdrawal
	Day 1				Day 3 - Day 21[2]							Every 7 days (up to Day 84)[2]	SOC Initiation[3]			
	Pre-Dose	Infusion/ Injection	In clinic follow-up[5]	24h	3	6	9	11	14	17	21					
ISR Assessment		X[7]	X[8]	X	X	X										Diary card to be distributed to subjects at Day 1 (see Section 8.3.8.1)
Acceptability of Treatment		X[7]											X	X		To be administered before any other assessments.
Laboratory Assessments																
Quantitative plasma HIV-1 RNA	X	X[7]	X[8]	X	X	X	X	X	X	X	X	X	X	X		
CCI																
PK Testing	X	X[7]	X[8]	X	X	X	X	X	X	X	X	X	X	X		GSK3810109A antibody concentrations in Serum. Each serum sample will be collected equally into 2 aliquots with one aliquot as a backup to be stored at sites and shipped later.
CCI																
Anti-drug antibody (ADA)	X											X[9]	X	X		
Whole Blood (PBMC)	X												X	X		
Lymphocyte Subset	X	X[7]	X[8]	X	X	X	X	X	X	X	X		X	X		
Safety Labs	X	X[7]	X[8]	X	X	X	X	X	X	X	X	X	X	X		Clinical chemistry, Hematology

Procedure	Monotherapy Phase (Part 1/ Part 2)[1]													ED	Follow-up[4]	Notes See also Section 8 for descriptions of assessments E.D = early discontinuation/withdrawal
	Day 1				Day 3 - Day 21[2]							Every 7 days (up to Day 84)[2]	SOC Initiation[3]			
	Pre-Dose	Infusion/ Injection	In clinic follow-up[5]	24h	3	6	9	11	14	17	21					
Fasting Labs	X												X	X		Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides
CCI																
Pregnancy test[11]	U/S			S	S	S	S	S	S	S	S	S	S	S	S	
Urinalysis	X												X	X		
COVID-19 [12]	X															
CCI																

1. The Schedule of Activities will be the same for Part 1 and Part 2 of the study, although doses and routes of administration may be different. In both Part 1 and Part 2, participants will remain in clinic from Pre-Dose for 4 hours for vital signs evaluation, regardless of randomized treatment assignment. An interim analysis and site communication will precede commencement of Part 2.
2. The minimum duration of the monotherapy phase is Day 11. The monotherapy phase will be extended with study visits conducted as listed through Day 21, and then every 7 days up to Day 84 in participants with data demonstrating that viral rebound has not occurred. In no case will the monotherapy phase extend beyond Day 84.
3. An SOC Initiation visit must be conducted in all participants and will be the last visit in the monotherapy phase. If the SOC Initiation visit coincides with a planned study visit (e.g. Day 11), the SOC Initiation will prevail, the SOC Initiation schedule of activities must be followed and the visit recorded as the SOC Initiation visit in the eCRF. The first dose of oral SOC combination ART should be given during this visit, after all other assessments and evaluations have been completed. The SOC Follow-Up Schedule of Activities will be followed for subsequent study visits. The SOC Initiation visit may be conducted as an unscheduled visit if results become available indicating that the participant has met the monotherapy endpoint criteria.
4. An in-clinic Follow-up Visit / phone call will be conducted only for participants with the following conditions at the last on-study visit: All ongoing SAEs and non-serious AEs of special interest (as defined in Section 8.3.8), regardless of attributability. However, the investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. The need for an in-clinic follow-up visit vs. a phone call will be determined by the Investigator based on the clinical status of the participant.

5. An in-clinic follow-up period is required for all study participants. The in-clinic follow-up period will last for 4 hours from the start of the infusion/ injection(s) and will include frequent vital signs monitoring as well as other clinical and laboratory evaluations.
6. Vital signs of blood pressure, heart rate, body temperature, respiratory rate and SpO2 will be measured every 15 minutes during GSK3810109 infusion, including at the conclusion of the infusion. For subcutaneous dosing, vital signs will be measured at the conclusion of SC dosing. In all dosing groups, vital signs will be measured at least every 30 minutes from the start of infusion/ injection for 2 hours, then every hour for another two hours. All vital signs should be recorded in the medical record and findings deemed clinically-significant by the Investigator must be reported as Adverse Events (Section 8.3).
7. Evaluations/blood draws to be conducted following the infusion/ injection.
8. Evaluations/blood draws to be conducted during the in-clinic follow-up period at 3 hours from start of infusion/ injection.
9. ADA samples will be collected at the Day 28, Day 56 and Day 84 study visits, if conducted, at the same time as the PK samples are collected.
10. Storage samples will be used as replacement samples if they are lost or arrive at the laboratory unevaluable or for additional evaluations as required.
11. At the Day 1 Visit (before start of study treatment), a urine (U) test must be used to confirm pregnancy status prior to administration of study treatment. Additionally, a serum sample will be sent for pregnancy testing at the same time. Pregnancy testing will be conducted on POCBP only on serum (S) samples.
12. COVID-19 testing will be PCR or antigen at Day 1 (pre-dose). COVID-19 PCR or antigen testing will be optional at all study visits should infection be suspected.

1.3.3. Standard of Care Follow-Up Phase Schedule of Activities

Procedure	SoC Oral Follow Up Phase (Weeks from End of Part 1/ Part 2)							E.D.	Follow-up[a]	E.D = early discontinuation/withdrawal Notes
	+1 week	+4 weeks	+8 weeks	+16 weeks	+24 weeks	+32 weeks	+48 weeks			
Clinical and Other Assessments										
Vital signs	X	X	X	X	X	X	X	X		blood pressure, heart rate and body temperature
Body Weight/ BMI					X		X	X		
HIV Associated Conditions		X	X	X	X	X	X	X		
Acceptability of Treatment					X		X	X		To be administered before any other assessments.
AE/SAE Review	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X		
Laboratory Assessments										
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X		
CCI [redacted]										
PK Testing	X	X	X	X	X	X	X	X		GSK3810109A antibody concentration in serum. Each serum sample will be collected equally into 2 aliquots with one aliquot as a backup to be stored at sites and shipped later
CCI [redacted]										
ADA sample		X	X	X	X	X	X	X		

Procedure	SoC Oral Follow Up Phase (Weeks from End of Part 1/ Part 2)							E.D.	Follow-up[a]	E.D = early discontinuation/withdrawal **Notes**
	+1 week	+4 weeks	+8 weeks	+16 weeks	+24 weeks	+32 weeks	+48 weeks			
CCI										
Lymphocyte Subset	X	X	X	X	X	X	X	X		
Safety Labs	X	X	X	X	X	X	X	X		Clinical chemistry and hematology
Fasting Labs					X		X	X		Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides
CCI										
Pregnancy test	S	S	S	S	S	S	S	S		S=serum
Urinalysis					X		X	X		
COVID-19 testing[c]										

a. An in-clinic Follow-up Visit / phone call will be conducted only for participants with the following conditions at the last on-study visit: All ongoing SAEs and non-serious AEs of special interest (as defined in Section 8.3.8), regardless of attributability. However, the investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

b. These samples will be used for viral geno/pheno (RT/PRO/IN) in event of virologic failure, as replacement samples if they are lost or arrive at the laboratory unevaluable or for additional evaluations as required.

c. COVID-19 PCR or antigen testing will be optional at all study visits should infection be suspected.

2. INTRODUCTION

Despite significant progress in the treatment and prevention of HIV infection, it has remained a significant public health problem since the virus was discovered in 1983. While current treatment and prevention options are effective, none of the current therapeutic or prophylactic regimens can completely prevent or cure an infection or induce a full recovery of the host immune system. Therefore, novel agents and strategies continue to be investigated.

Broadly neutralizing antibodies (bNAb) reactive to viral proteins expressed by circulating virus hold the promise as effective therapeutic or prophylactic agents against HIV. Several broadly neutralizing human monoclonal antibodies have been isolated and are in various stages of development for treatment and prevention of HIV infection. These include antibodies with specificities to the CD4 binding site (VRC01 [Bar, 2016], VRC07-523LS [Kwon, 2012], 3BNC117 [Scheid, 2011]), the high mannose patch (10-1074 [Mouquet, 2012], PGT121 [Walker, 2011]), the V2 apex (PG9 [Walker, 2009] [McLellan, 2011], PDGM 1400 [Walker, 2011], CAP256.25 [Doria-Rose, 2015]) and the membrane-proximal external region (10E8 [Kwon, 2016]).

N6 is a broadly neutralizing HIV antibody that has shown high potency against various HIV isolates, including strains that are resistant to other antibodies. N6 was isolated from a patient with a 21-year known history of HIV-1 infection that was controlled in the absence of HAART [Huang, 2016] and is in the class of bNAbs that targets the CD4-binding site of the HIV envelope protein by occluding the binding site for the cellular receptor CD4.

In order to improve the pharmacokinetics of N6, two amino acid substitutions (methionine to leucine and an asparagine to serine) were introduced within the C-terminus of the heavy chain region of N6 via site-directed mutagenesis to increase its binding affinity for the neonatal Fc-receptor. Incorporation of the LS mutations did not affect the neutralization breadth or potency of N6LS compared to N6 [Huang, 2016].

Based on preclinical and clinical studies of other bNAbs with and without the LS mutation [Rudicell, 2014; Ko, 2014; Gaudinski, 2018], the LS modification is expected to result in enhanced recirculation and longer plasma half-life of N6LS relative to the wild-type antibody (N6). N6LS (GSK3810109A) is being developed for the treatment of HIV-1 infection in adults in combination with other agents.

2.1. Study Rationale

This Phase 2a proof of concept (PoC) trial will be the first study of GSK3810109A (N6LS) in HIV-infected participants and will evaluate the efficacy, safety, tolerability, and pharmacokinetics of the broadly neutralizing HIV antibody GSK3810109A in treatment naïve viremic adults after a single dose administered as infusion or SC injection. Data from this study will be utilized to select doses and routes of administration for further studies of GSK3810109A in combination with other ART in Phase 2b and beyond.

2.2. Background

GSK3810109A belongs to a class of broadly neutralizing HIV antibodies (bNAb). These antibodies target the CD4-binding site of the HIV envelope protein. A detailed description of the chemistry, pharmacology, and data from the first time in human (FTIH) study (Protocol VRC609) is provided in the GSK3810109A Investigators Brochure.

Protocol VRC609, the FTIH study of GSK3810109A in healthy individuals assessed the safety, tolerability and pharmacokinetics of this antibody. The FTIH study was an open-label, single and repeat dose administration of N6LS given across 6 dose groups of either a single IV infusion at 5, 20, or 40 mg/kg dose levels (N=3 for each group), a single SC injection at the 5 mg/kg dose level (N=3), in 3 administrations 12 weeks apart by SC injection at the 5 mg/kg dose level (N= 5) or in 3 administrations 12 weeks apart by IV infusion at the 20 mg/kg dose level (N=5). Enrolment was completed with 22 participants enrolled and all participants have completed dosing.

GSK3810109A was generally well tolerated, with no SAEs, dose-limiting toxicities or deaths reported. Treatment-emergent laboratory abnormalities have been few and mostly Grade 1. Data from the FTIH study was utilized to support future clinical development of GSK3810109A and determined the starting doses to be used in Part 1 of 207959.

The current study, 207959, is designed based on the known data from GSK3810109A along with experiences from other CD4-binding site bNAbs VRC01 [Lynch, 2015] and 3BNC117 [Caskey, 2015] as well as the modified versions of VRC01LS and VRC07-523LS which are designed for extended serum half-life by increased binding affinity to the neonatal Fc receptor, which are similar to GSK3810109A [Gaudinski, 2018] [Gaudinski, 2019].

These other bNAbs were administered at similar doses, frequency and routes as GSK3810109A in the FTIH VRC609 study and have been generally well-tolerated with no deaths or serious adverse events assessed as related to the investigational drug. The predominant local reactogenicity complaint has been mild pain/tenderness, although reports of mild injection site pruritus, redness and swelling have occurred at modestly higher frequencies with the SC administration. Malaise, muscle pain and headache have been the most frequently reported events noted in the 3 days post product administration. These events have been mild in severity and transient. Although infrequent, infusion reactions comprised of chills, rigors, myalgia, and headache have been reported after IV infusions at product doses of 10 to 40 mg/kg. These reactions have been transient, resolving within 24-hours of onset, without sequelae, and have generally been treated with over-the-counter analgesics and antipyretics.

This Phase 2a proof of concept (PoC) trial will be the first study of GSK3810109A in HIV-infected participants and will evaluate the efficacy, safety, tolerability, and pharmacokinetics of the bNAb GSK3810109A in antiretroviral-naïve, viremic adults following a single dose infusion or single dose subcutaneous injection.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3810109A may be found in the GSK3810109A Investigator's Brochure.

In the first time in human study (Protocol VRC609), no SAEs or deaths were reported and no withdrawals were due to drug-related AEs. All reported AEs were either Grade 1 or 2. Furthermore, there was no evidence of a dose or administration route relationship with regard to AEs.

The safety concerns identified for N6LS from non-clinical toxicology studies and limited clinical data from the VRC Phase 1 clinical trial include: local/systemic reactogenicity, liver chemistry elevations, neutropenia, serious/severe immune reactions and immunogenicity. The main safety concern in this single dose study in HIV-infected treatment-naïve participants are local and systemic reactogenicity. These reactions are to be expected due to the route of administration and in the Phase 1 study were transient, without sequelae, and treated with over the counter analgesics and antipyretics. With the implementation of appropriate risk mitigation strategies, all safety concerns are considered manageable (see Section 2.3.1).

To ensure the overall safety of participants this clinical trial will include participants who will receive clinical, laboratory, and safety assessments prior to and during their participation in the trial. Furthermore, a Safety and Dose Evaluation Committee (SDEC) will review emerging data and make recommendations per the Go/No Go criteria included in this protocol, recommend study changes, including doses and routes of administration for Part 2, and review safety parameters during the course of the study.

2.3.1. Risk Assessment

The following table outlines the risk assessment and mitigation strategy for this protocol. Additionally, all participants will be closely monitored over the 11 days (minimum monotherapy duration) following the administration of a single dose of GSK3810109A. During the Standard of Care follow-up phase, all participants will be placed on an oral integrase-based combination ART with frequent monitoring at approx. 1, 2, 4, 6, 8, and 12 months after the monotherapy phase.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3810109A		
Serious/severe immune reactions **(Anaphylaxis and Cytokine release syndrome [CRS])**	**Non-clinical** No serious/severe immune reactions noted in the non-clinical rat study **Clinical** Administration of mAbs may cause immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine monoclonal antibodies which would have a risk of human anti-mouse antibodies. CRS reactions most commonly occur within the first few hours of beginning the infusion and are more	Anaphylaxis is a life-threatening reaction with respiratory, cardiovascular, cutaneous, or gastrointestinal manifestations. Vital signs will be monitored during the infusion and prompt treatment of anaphylaxis is critical, with subcutaneous or intramuscular epinephrine and intravenous fluids. Adjunctive measures include airway protection, antihistamines, steroids, and beta agonists. Some symptoms may be treated by slowing or stopping the infusion. Supportive treatment may also be indicated for some signs and symptoms. Patients with anaphylaxis should be closely monitored for the possibility of recurrent symptoms after initial resolution.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	common with the first mAb infusion received. This is because cytokine release is associated with lysis of cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb. GSK3810109A is expected to have a low risk for serious/severe immune reactions as it is directed against a viral antigen and is human in origin. No serious/severe immune reactions have been previously observed with GSK3810109A.	Urinary and serum histamine levels and plasma tryptase levels drawn after onset of symptoms may assist in diagnosis **In stream study pause criteria (participant level):** Acute Allergic reaction or cytokine release syndrome (DAIDS criteria Grade 3-4) reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator and Sponsor
Local reactogenicity (injection site reactions)	**Non-clinical** The repeat dose IV and SC administration of GSK3810109A at 40 and 400 mg/kg (IV) and 5 and 50 mg/kg (SC) in male and female Sprague-Dawley rats produced test article-related effects in injection site irritation (slight erythema observed with low incidence, reversible, considered not toxicologically relevant). **Clinical** All reported instances of local reactogenicity (pain/tenderness, swelling, redness, bruising, pruritus) were mild (Grade 1) except for one moderate (Grade 2) instance each of swelling and redness. All local	Exclusion criteria as described in Section 5.2 will prohibit participants with an underlying skin disease or disorder (i.e. infection, inflammation, dermatitis, eczema, drug rash, drug allergy, psoriasis, food allergy, urticaria) that would interfere with assessment of injection sites. Participants will be closely monitored for local/systemic reactions. Administration advice to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs given in study documentation

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reactogenicity events were reported as recovered within 5 days of onset.	Advice to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate
	The most frequently reported event was Grade 1 pain/tenderness at the injection site in the SC groups (6/8, 75%). Overall, there was more reactogenicity in the SC groups (16 reactions over 18 administrations) versus the IV groups (1 reaction over 24 administrations)	AEs Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored. Significant ISRs will be photographed and referred to a dermatologist for specialist advice and possible biopsy. **In stream study pause criteria (participant level):** Any Grade 4 AE assessed as related to GSK3810109A by the Investigator Or Any Serious Adverse Event (SAE), regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator or Sponsor.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		In stream study pause criteria (cohort level): If ≥30% of participants within a dose group have a Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) once half of study participants have been dosed.
Systemic reactogenicity	**Non-clinical** In the repeat dose study in Sprague Dawley rats of 3-weeks duration, two females given 40 mg/kg/IV showed hypoactivity and prostrate posture on Day 21 immediately and/or 2-4 hours post dose with recovery within 24 hours, consistent with an infusion related reaction. **Clinical** All reported instances of systemic reactogenicity (malaise, myalgia, headache, nausea, chills) were mild (Grade 1) and were reported as recovered within 1 day of onset.	Participants will be closely monitored for local/systemic reactions. IV access will be placed in an arm vein in an aseptic manner. GSK3810109A will be administered with approximately 100 mL of normal saline IV over 1 hour minutes. Infusions lasting longer than 1 hour are allowed. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms. Vital signs will be monitored during infusions. **In stream study pause criteria (participant level):** Any Grade 4 AE assessed as related to GSK3810109A by the Investigator Or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The most frequently reported event was Grade 1 headache in 1/8 (13%) participant in the SC groups and 4/14 (27%) participants in the IV groups. Overall, there was more systemic reactogenicity in the IV groups (7 reactions over 24 administrations) versus the SC groups (4 reactions over 18 administrations).	Any Serious Adverse Event (SAE), regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator or Sponsor. **In stream study pause criteria (cohort level):** If ≥30% of participants within a dose group have a Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) once half of study participants have been dosed.
Gastrointestinal disorders **(Diarrhea)**	**Non-clinical** N/A **Clinical** In the phase 1 study, three participants experienced diarrhea (Grade 1 - Grade 3) considered related by the Investigator. Time to onset was 1 to 6 days from last dose and all recovered within 2 days. One additional participant with Grade 1 diarrhea was not considered related (time to onset was 19 days post dose).	Careful monitoring of adverse GI events will occur throughout the study. Serious/severe events will be managed appropriately and will be followed to resolution as per standard ViiV Medical Monitoring practices. **In stream study pause criteria (participant level):** Any Grade 4 AE assessed as related to GSK3810109A by the Investigator Or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Any Serious Adverse Event (SAE), regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator or Sponsor. **In stream study pause criteria (cohort level):** If ≥30% of participants within a dose group have a Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) once half of study participants have been dosed.
Liver chemistry elevations	**Non-clinical** The repeat dose IV and SC administration of GSK3810109A at 40 and 400 mg/kg (IV) and 5 and 50 mg/kg (SC) in Sprague-Dawley rats produced test article-related effects in clinical chemistry with up to 1.5-fold increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP), correlating with the histopathologic findings in the liver, within high-end of normal ranges and considered not to have reached a level of toxicity.	**Exclusion criterion for Phase 2a:** participants with liver impairment based on screening liver chemistry: Participants with ALT>1.5 ULN or total bilirubin >1.5 ULN are excluded. Liver transaminases (ALT and AST) will be monitored throughout this study (refer to SoA, Section 1.3) and the liver chemistry stopping criteria will be adopted as described in Section 7.3 of this protocol. **In stream study pause criteria (participant level):** Phase 2a liver chemistry stopping criteria:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical A total of 3 (14%) participants experienced liver enzyme elevations: 2 ALT elevation; 1 AST elevation. All Grade 1 or 2) and transient.	• ALT≥3xULN • If ALT≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin), i.e. Hy's case, report event as SAE. **In stream study pause criteria (cohort level):** If ≥30% of participants within a dose group have a Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) once half of study participants have been dosed.
Neutropenia	**Non-clinical** The repeat dose IV and SC administration of GSK3810109A at 40 and 400 mg/kg (IV) and 5 and 50 mg/kg (SC) in Sprague-Dawley rats produced test article-related effects in monocytes up to 2.6-fold increase, reticulocytes up to 3.7-fold increase and eosinophils up to 72.7% decrease, all reversible, correlated with non-adverse histopathology findings in axillary lymph nodes, spleen and bone marrow and/or organ weight findings in spleen.	Close monitoring of blood counts in participants initiating therapy will be conducted throughout this study (refer to SoA, Section 1.3). **In stream study pause criteria (participant level):** any Grade 4 AE assessed as related to GSK3810109A by the Investigator. Or Any Serious Adverse Event (SAE), regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator or Sponsor.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical A Grade 2 neutropenia in 1/22 participant was considered possibly related by the Investigator in the Phase 1 study. Baseline neutrophil count was 3.15 x 103 cells/μL. Neutropenia (0.75 x 103 cells/μL) started 23 days post dose (single IV dose (20 mg/kg) and returned to 3.11 x 103 cells/μL (within normal range) 13 days later at the next specimen collection. No intercurrent illness or confounding concomitant medication was reported.	**In stream study pause criteria (cohort level):** If ≥30% of participants within a dose group have a Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) once half of study participants have been dosed.
Immunogenicity	**Non-clinical** GSK3810109A exhibited lower serum concentrations after repeat administration via both routes in the dose ranges studied suggesting the formation of anti-drug antibodies which was more prominent in the SC dose groups but also apparent in the 40 mg/kg IV dose group. Following repeated administration of 400 mg/kg IV during the main study there was faster clearance in some animals by Day 56. In addition, two females given 40 mg/kg/IV showed hypoactivity and prostrate posture on Day 21 immediately and/or 2-4 hours post dose with recovery within 24 hours, consistent with an infusion related reaction. The toxicities observed are therefore considered possibly to be a result of the formation and subsequent clearance of anti-drug	The emergence of ADAs will be actively monitored using a validated ADA assay (screening, confirmation, and titration).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	antibodies (ADAs), although this cannot be confirmed since immunogenicity analysis was not conducted. **Clinical** Animal studies are generally not predictive of immunogenicity and sequelae related to immunogenicity in humans. ADAs were detected in 2/22 (9%) of GSK3810109A-treated subjects at any time after dosing, however, exhibited no neutralizing activity. There were no discernible effects of immunogenicity on the safety and PK profiles from the Phase 1 study.	

2.3.2. Benefit Assessment

This study in treatment naïve, HIV-1 infected participants includes a single dose monotherapy phase in both Part 1 and Part 2 which includes frequent site visits and close monitoring for new signs and symptoms following a single dose infusion or single dose SC injection. The monotherapy period uses a response-guided approach so that participants will initiate combination antiretroviral therapy (cART) as soon as possible following necessary evaluations to fully characterize the potency and duration of virologic effect of GSK3810109A. While no direct benefits should be expected for study participants in this part of the study, the information learned may help others living with HIV, and help advance new long-acting treatments for people living with HIV.

A Go/No-Go decision (see Section 9.5) to progress to Part 2 will be based on the virologic response from the 40 mg/kg IV dose group and the safety data from both dose groups in Part 1. The Safety and Dose Evaluation Committee (SDEC) will review emerging data from the two dose groups in Part 1 in order to select appropriate doses and routes of administration for Part 2.

During the standard of care follow-up period all participants will initiate an integrase-based oral combination therapy to treat their HIV and be monitored for an additional 48 weeks. Oral HIV treatment with fixed-dose dolutegravir + lamivudine will be provided through the study for use during the follow-up period.

2.3.3. Overall Benefit: Risk Conclusion

Given the non-clinical and clinical profile to date, data from other bNAb studies, the frequent visit schedule, and the proposed dose levels in the single dose monotherapy phase, the overall risk to treatment-naïve HIV-1 infected participants in this study is predicted to be low and manageable.

Additionally, the doses administered in this study will not exceed those in the FTIH study (VRC609), see Section 2.2 for additional information on this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the antiviral activity following a single dose of GSK3810109A in treatment-naïve HIV-1 infected participants	Plasma HIV-1 RNA maximum change from Baseline during the monotherapy phase
• To assess safety parameters following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Adverse events, Grade 2-4 ALT/ AST, treatment-emergent ECG abnormalities and Grade 2-4 injection site reactions

Objectives	Endpoints
Secondary	
• To characterize the pharmacokinetics of GSK3810109A in treatment-naïve HIV-1 infected participants following a single IV or SC administration	• GSK3810109A PK parameters following single dose administration e.g.: AUC (0-t), Cmax, Tmax, Ct
• To explore the potency of GSK3810109A	Relationship between GSK3810109A exposure and change in plasma HIV-1 RNA over time.
• To assess the immunologic changes following a single IV or SC dose of GSK3810109A	Absolute values and change in T cell counts from baseline over time
• To assess whether anti-drug antibodies develop following a single dose of GSK3810109A	Incidence of and titre in serum of anti GSK3810109A antibodies over time
Safety	
• Safety and tolerability of GSK3810109A following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Clinical laboratory parameters, ECGs, vital signs, and injection site reactions over time.
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI	

4. STUDY DESIGN

4.1. Overall Design

Protocol 207959 is a two-part, randomized, open label adaptive design study to characterize the antiviral activity, safety/tolerability, PK and PK/Pharmacodynamics (PD, HIV-1 RNA decline) of GSK3810109A administered both intravenously (IV) and subcutaneously (SC) in HIV-1 infected, treatment-naïve adults. The study design includes a screening phase, a randomized monotherapy phase and a standard of care follow-up phase. The two parts of the randomized phase will each include a single dose monotherapy evaluation period after which all participants will enter a long-term follow-up period during which participants will initiate an appropriate integrase-based standard of care treatment regimen.

4.1.1. Screening Phase

Informed consent must be obtained prior to any study procedures, including any Screening assessment.

Participants will complete a screening period of up to 28 days. Screening may be extended up to one additional week if lab results are pending (randomization or screen failure must occur within 35 days following the Screening Visit). A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). Participants may be re-screened once which requires a new participant number. Participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be randomized on Day 1 as soon as all eligibility requirements have been confirmed at the site.

4.1.2. Randomized Monotherapy Phase

The randomized phase will occur in Part 1 and, if pre-defined Go/No Go criteria are met, Part 2.

Part 1 will include 2 dose groups administered as a single IV infusion of either 40 mg/kg or 280 mg flat dose (representing approximately 4 mg/kg for an average 70 kg individual). Randomization will be balanced (1:1) into the two dose groups in Part 1.

Part 2 is anticipated to include 3 dose groups (but may include up to four dose groups dependent upon data generated from Part 1) administered as a single IV infusion or SC injection (the SC dose may require multiple injections given at one time). Randomization will be balanced into each of the dose groups selected for Part 2.

An interim analysis will be conducted from data obtained during the Part 1 monotherapy period (Groups 1 and 2) and available data from ongoing SOC, in which virologic response, safety and PK will be evaluated. The interim analysis will be conducted according to criteria defined in Section 4.4 and Section 9.5. Further groups will then be studied in Part 2 across a range of up to 4 additional dose levels. Final doses and administration routes in Part 2 will be determined following evaluation of data from Part 1.

An SDEC will review data from Part 1 and determine study progression based upon the pre-defined Go/No Go criteria. The SDEC will also determine dosing in Part 2. In Part 2, GSK3810109A will be administered either intravenously or subcutaneously.

4.1.3. Standard of Care Follow-Up Phase

Following the monotherapy period, a standard of care integrase-based treatment regimen will be initiated and maintained for the duration of the long-term follow-up period. Virologic response, safety and PK will continue to be assessed during the follow-up period. Assessments of tolerability, acceptability and markers of immune function will also be collected throughout the study.

A SOC Initiation visit will be conducted in all participants at the conclusion of the monotherapy period. The SOC is stipulated to be an integrase inhibitor-based cART regimen, and must be initiated the day of the SOC Initiation visit. A regimen of dolutegravir + lamivudine will be provided through the study if deemed appropriate by the investigator and consistent with local guidelines. Alternative integrase inhibitor-based cART regimens may be permissible for use during the SOC follow-up phase after consultation and agreement with the medical monitor. Alternative SOC regimens will not be provided through the study and must be procured locally. A plan for SOC therapy should be considered at the time participants are screened to assure that an appropriate SOC regimen is selected and available prior to randomization into the monotherapy phase of the study. Reimbursement for alternative SOC regimens may be available, where agreed in advance with the medical monitor.

4.2. Scientific Rationale for Study Design

Previous studies with bNAbs have found that HIV-1 RNA nadir was achieved after 7-10 days of dosing (VRC01 – day 9 [Lynch, 2015], 3BNC117 – day 7 [Caskey, 2015], 10-1074 – day 10.3 [Caskey, 2017]).

Study 207959 is a Phase 2a, open label, single dose study evaluating up to 6 IV or SC dose levels of GSK3810109A, including a maximum 40 mg/kg dose. A Go/No Go decision to progress to Part 2 will be based on the virologic response from the 40 mg/kg infusion dose group of Part 1, see Section 4.4 and Section 9.5 for additional information.

Study 207959 will include a monotherapy period following a single dose to determine antiviral activity and characterize viral dynamics. Emerging data from the two IV dose levels in Part 1 will be utilized to select appropriate doses and administration routes for Part 2. If SDEC review determines that criteria to continue are met, additional

participants will be enrolled in Part 2 and receive GSK3810109A ≤40 mg/kg given as a single dose infusion or SC injection.

Study 207959 is designed to evaluate safety, PK and virologic endpoints when GSK3810109A is administered both via IV infusion and by SC injection. The inclusion of both routes of administration in this study is an efficient design to enable rapid progression to Phase 2b in either or both routes of administration. Further, subsequent studies of GSK3810109A are envisioned to be conducted in a stably suppressed HIV-infected patient population. Therefore, the inclusion of both IV and SC administration in the current study enables evaluation of these endpoints by both routes of administration, including exploratory immunologic endpoints, in an ART-naïve, HIV-infected population.

207959 is designed as an open-label study; an open label trial design affords the availability of real time safety data following antibody infusions. Based upon the small sample size (approximately 10 participants for all Groups in Part 1 and Part 2) and the open-label trial design, safety and tolerability will be assessed in-stream (via a Safety Review Team) as well as at defined analysis timepoints (via the Safety and Dose Evaluation Committee). Enrollment in Part 1 will continue until approximately 10 evaluable participants are confirmed in Group 1. If participants prematurely discontinue during Part 1 or Part 2 additional replacement participants may be enrolled at the discretion of the Sponsor. These replacement participants will be assigned to the same dose as the corresponding participant who prematurely discontinued from the study.

Consistent with other proof of concept studies of CD4 binding site bNAbs, no placebo arm is included in this study [Bar, 2016; Gaudinski, 2019]. The FTIH (VRC609) has provided supportive data on the safety and tolerability of GSK3810109A at similar exposures to those planned in this study, supporting progression without the need for a control group for safety comparisons. A placebo control group would not be expected to improve interpretation of the PK or virologic endpoints, which are laboratory-derived. Furthermore, current clinical practice recommends immediate initiation of combination antiretroviral therapy (cART) at the time of diagnosis; inclusion of a placebo group would delay the initiation of cART in those participants without expected scientific benefit.

The monotherapy period in Part 1 and Part 2 is designed to balance a minimum duration to observe viral activity (viral nadir) of GSK3810109A with the need to initiate standard of care therapy as soon as possible. A minimum monotherapy period has been established to observe virologic response in all participants, even where modest or non-response may occur. In this study with frequent follow-up visits, a minimum monotherapy period of 11 days will yield at least 4 assessments to evaluate viral dynamics of GSK3810109A prior to initiation of SOC cART, with a high likelihood to observe viral nadir based on data from other CD4 binding site bNAbs.

A response-guided algorithm will be used to determine initiation of SOC cART in participants with a more robust virologic response. In those participants, the monotherapy period will be extended until virologic rebound is achieved, up to Day 84. A response-guided extension of the monotherapy period allows for a more complete characterization

of the viral nadir, thus aiding in final dose, dose frequency and administration route selection.

Participants should continue in the monotherapy period until meeting one of the following monotherapy endpoint criteria, which are assessed at each study visit beginning at Day 11:

1. Virologic non-response. Virologic non-response will be confirmed if, at Day 11, viral nadir decline is $<0.5\log_{10}$. Viral nadir is defined as the lowest observed post-Dose HIV-1 result and viral nadir decline is calculated from the Day 1 (Pre-Dose) HIV-1 RNA result.

2. Virologic rebound. Virologic rebound will be confirmed if either of the following have occurred at or after Day 11:

    - HIV-1 RNA rebound of $\geq 1.0\log_{10}$ increase from nadir.

    - HIV-1 RNA rebound to $<0.5\log_{10}$ from Baseline. This criteria will be met where there is a rebound from nadir that is less than $1.0\log_{10}$, but within 0.5 $\log_{10}$ of the Day 1 (Pre-Dose) study visit.

3. Missing/delayed data from previous visits. HIV-1 RNA results are generally expected to be returned within 48-72 hours from the central lab, however, a delay can impede the ability to determine a study participant's status to continue in monotherapy or initiate SOC cART. This is especially important during the first 21 days of the monotherapy period where study visits are frequent and results from the immediately preceding visit may not be available. In cases where HIV-1 RNA results are not yet available, monotherapy endpoint status is generally to be determined from available results at the time of study visits, but must be reviewed and agreed with the study medical monitor prior to initiation of SOC cART.

4. Day 84. In no instance will the monotherapy period go beyond Day 84, even if virologic rebound criteria have not been met. The SOC Initiation visit must be conducted in all participants no later than Day 84.

A standard of care cART regimen will be initiated in all study participants at end of the monotherapy period in Parts 1 and 2 in order to both limit the potential development of resistance or reduced susceptibility to GSK3810109A as well as to meet the desire to initiate cART as soon as possible in these antiretroviral-naive HIV-infected participants. An integrase-based regimen is further stipulated in this study due to the very rapid viral suppression typically seen with this class of antiretroviral agents, thus achieving these two objectives as quickly as possible following the monotherapy period in Parts 1 and 2.

Participants who receive GSK3810109A will continue to be followed for safety purposes according to the study schedule of activities. Participants will not be discontinued or replaced in the study for initiating or changing ART during the SOC follow-up period (including substitution of a non-integrase-based regimen, if deemed appropriate by the principal investigator) and will continue to be followed for safety purposes according to the study schedule of evaluations. ART regimen changes will be documented in the

participant's record. Oral dolutegravir + lamivudine (Dovato™) will be provided in the study for use during the SOC follow-up period, if appropriate and consistent with local Guidelines.

Initiation of an integrase-based ART is expected to occur immediately after participants complete the monotherapy study evaluations. Participants who remain viremic on antiretroviral therapies (ARTs) will be encouraged to talk to their primary care provider about their ARV regimen, per local guidelines (Department of Human and Health Services (DHHS) guidelines [DHHS, 2019] in the US).

4.3. Justification for Dose

The dose range for investigation in this study is defined by PK data from healthy volunteers (Study VRC609) and preclinical potency data. Based on in vitro experiments, the estimated 90th percentile of GSK3810109A potency (IC90) is ~ 10 µg/mL. The observed preliminary exposures at day 14 at the clinical doses studied and the overages compared to the IC90 values in FTIH study (Study VRC609) are listed in Table 1. The recommended starting doses of 280 mg and 40 mg/kg in Part 1 of the current study reflect the dose range of approximately 5 – 40 mg/kg doses studied in the FTIH study and thereby provides systemic GSK3810109A exposures at day 14 that are approximately 1X and 32X fold above the IC90 respectively. Additionally, the dose range to be evaluated is selected to allow adequate characterization of the exposure-response relationship between GSK3810109A exposures and viral load changes.

Table 1 Observed preliminary exposures at Day 14 from Study VRC609

Dose (mg/kg)	Concentration on day 14 (Mean (SD) µg/mL)	IC90 Overage
5 mg/kg SC	16.9 (3.9)	>1.5X
5 mg/kg IV	21.6 (2)	>2X
20 mg/kg IV	171.8 (52.5)	>17X
40 mg/kg IV	326.6 (71.7)	>32X
Preliminary PK data from Study 609 VRC (n=3 for each of these dose groups)		

In addition, there are other bNAbs that are administered at similar doses, frequency and routes as GSK3810109A in the FTIH VRC609 study and have been generally well-tolerated with no deaths or serious adverse events assessed as related to the investigational product.

Part 1, Group 1 (high dose group) will evaluate an IV infusion of GSK3810109A (40 mg/kg) that has been previously tested in the prior Phase 1 study (VRC609, Section 2.2). This dose is targeted to achieve the maximum anticipated reduction of HIV-1 RNA and was well-tolerated with a single IV administration in the FTIH VRC609 study. This is the highest dose to be tested in this study.

Part 1, Group 2 will assess GSK3810109A administered at a lower flat dose (280 mg) IV infusion. The doses in Part 1 are selected to allow full characterization of single-dose antiviral activity and to select optimal doses for the subsequent study groups in Part 2.

For more information on data from the FTIH study with GSK3810109A and clinical data from other bNAbs see Section 2.2.

Doses in Part 2 of this study may be modified based on the data from Part 1, see Section 6.9 for more information.

4.4. Interim Go / No Go Criteria and Dose Selection for Part 2

In this study, a <0.5 $\log_{10}$ decrease will serve as the no effect threshold for antiviral effect. This is in line with the variation of <0.5 $\log_{10}$ HIV-1 RNA observed in serial viral load measurements from chronic HIV-1 infected patients, serves as an intra-person control, and would obviate the need for a placebo arm. [Holodniy, 1994; Lima, 2017].

The efficacy Go or No-Go criteria will use a $\log_{10}$ nadir viral load decline (Δ) at the highest IV dose (Part 1, Group 1) to predict population average nadir viral load decline. A minimum value (MV) for viral load decline was set at $\Delta = 1$ $\log_{10}$. The target value (TV) viral load decline was based on historical bNAb POC data and was set at $\Delta =$ 1.3 $\log_{10}$ if all participants are considered and $\Delta = 1.4$ $\log_{10}$ if only viral load responders are considered. The specific criteria for the interim decision criteria are detailed in Section 9.5.

Emerging viral load data at the two dose levels in Part 1 i.e. the $\log_{10}$ nadir viral load decline (Δ) and the viral kinetics i.e. time to reach viral nadir and rebound, as well as key safety elements, will be utilized to select appropriate doses for Part 2 of the study. The doses will be selected to allow adequate characterization of the exposure-response relationship between GSK3810109A and viral load decline.

At the Part 1 interim analysis stage, safety Go / No-Go criteria are pre-defined as:

No Go:

- If ≥35% of treated participants in Part 1 receiving GSK3810109A have a clinically significant Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) determined by the SDEC

Go:

- The above safety 'no go' criteria is not met.

The safety interim analysis will be based on all available safety data from the monotherapy phase of Part 1 participants at the time of the interim efficacy data cut-off. >65% of Part 1 participants must complete monotherapy without a clinically significant Grade 3 or lab abnormality trend before the study can proceed with Part 2 (Go decision). Additional ongoing safety data from Part 1 participants through the monotherapy phase completion will be added to the interim safety analysis until a definitive decision (Go or No Go) can be reached.

If a No Go decision is reached, the study will be stopped and no additional cohorts will be recruited.

4.5. End of Study Definition

A participant is considered to have completed the study if he/she has completed all assessments in the Monotherapy Phase and the SOC follow-up phase shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the SOC follow-up phase of the study or last scheduled procedure shown in the SoA for the last participant in the trial.

The SoA can be found in Section 1.3.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants must have documented HIV-1 infection at the Screening Visit:
   - Plasma HIV-1 RNA ≥5000 c/mL.

   NOTE: A single repeat test is allowed to determine eligibility. An HIV-1 RNA result ≥5000 c/mL will serve as confirmation of HIV-1 infection.
3. Screening CD4+ T-cell count ≥ 250 cells/mm^3:

   NOTE: A single repeat test is allowed to determine eligibility.
4. Antiretroviral naïve: No ARTs (in combination or monotherapy) received after the diagnosis of HIV-1 infection:

   Participants who received HIV post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) in the past are allowed as long as the last PEP/PrEP dose was >6 months from HIV diagnosis or there is documented HIV seronegativity at least 2 months after the last prophylactic dose and prior to the date of HIV diagnosis. The study site must have viewable documentation of the seronegative test available and placed into the study source documents.

Weight

5. Body weight ≥50 kg to ≤115 kg

Sex

6. Male and/or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

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

a. Participants **who are female at birth** are eligible to participate if at least one of the following conditions applies:

- Not Pregnant or breastfeeding and at least one of the following conditions applies:
  - Is not a participant of childbearing potential (POCBP).

    OR

  - Is a POCBP and using an acceptable contraceptive method as described in Section 10.5.2 during the intervention period (at a minimum until after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- A POCBP must have a negative highly sensitive (see Section 10.5.2) pregnancy test (urine or serum as required by local regulations) on Day 1, prior to the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 1.3.
- All participants in the study should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Contraception Guidance and Collection of Pregnancy Information can be found in Section 10.5.

QTc

7. QTc Interval ≤450 msec.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Participants with primary HIV infection, evidenced by acute retroviral syndrome (e.g., fever, malaise, fatigue, etc) and/or evidence of recent (within 3 months) documented viremia without antibody production and/or evidence of recent (within 3 months) documented seroconversion.
2. Participants who are pregnant, breastfeeding, plan to become pregnant or breastfeed during the study.
3. The participant has an underlying skin disease or disorder (i.e. infection, inflammation, dermatitis, eczema, drug rash, drug allergy, psoriasis, food allergy, urticaria) that would interfere with assessment of injection sites.
4. Known history of cirrhosis with or without viral hepatitis co-infection.
5. History of clinically relevant hepatitis within last 6 months.
6. Evidence of Hepatitis B virus (HBV) infection based on the results of testing at screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antigen antibody (anti-HBs) and HBV DNA as follows:
    - Participants positive for HBsAg are excluded.
    - Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded.

Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and negative for HBV DNA are not excluded.

Note: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded.

7. Patients with Hepatitis C co-infection.
8. Untreated syphilis infection (positive rapid plasma reagin (RPR) at screening) without documentation of treatment. Participants who are one month post completed treatment are eligible if recruitment is open.
    - Rescreening is allowed after treatment.

9. Prior receipt of licensed or investigational monoclonal antibody.
10. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy.
11. Known or suspected moderate or severe hepatic impairment (Class C as determined by Child-Pugh Classification, Section 10.9) coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
12. Clinically significant cardiovascular disease, as defined by history/evidence of congestive heart failure, symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease at the discretion of the investigator.
13. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the study medical monitor for inclusion of the participant prior to randomization.
14. Any pre-existing physical or mental condition which, in the opinion of the investigator, may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations, or which may compromise the safety of the participant;
15. Participants with substance abuse disorders or social restraints that the investigator considers to be possible deterrents to successful completion of the study.
16. Participants who in the investigator's judgment, pose a significant suicidality risk. Participants' history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk.
17. History of sensitivity to any of the study medications or their components or drugs of their class, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
18. Any condition which, in the opinion of the investigator, may interfere with the absorption, distribution, metabolism or excretion of the study drugs, combination ART or render the participant unable to take oral medication.
19. Participants with a positive COVID-19 test at Screening. Participants with known COVID-19 positive contacts within the past 14 days, or with symptoms suggestive of active COVID-19 (fever, cough, myalgias, shortness of breath, loss of taste or smell), should be excluded. Participants who remain symptom-free for at least 14 days after a COVID-19 exposure are allowed.

Prior/Concomitant Therapy

20. Has received any HIV-1 immunotherapeutic vaccine or prophylactic vaccine.

21. Treatment with any of the following agents within 28 days of screening:

    - radiation therapy;
    - cytotoxic chemotherapeutic agents;
    - any systemic immune suppressant;

22. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP.
23. Participants receiving any prohibited medication and who are unwilling or unable to switch to an alternate medication.

Prior/Concurrent Clinical Study Experience

24. Participant enrolled in a prior or concurrent clinical study that includes a drug intervention within the last 30 days.

Diagnostic assessments

25. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator, would preclude the participant's inclusion in the study of an investigational compound.
26. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening period to verify a result.
27. Alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal (ULN).
28. Total Bilirubin ≥1.5 times the ULN.
29. Creatinine clearance of <50 mL/min/1.73 m^2 via CKD-EPI method.
30. Hemoglobin ≥Grade 2 (Males: <10 g/dl; Females <9.5 g/dL). A single repeat test is allowed during the Screening period to verify a result.
31. Platelets ≥Grade 2 (<100,000 cells/mm^3). A single repeat test is allowed during the Screening period to verify a result.
32. PT ≥Grade 2 (≥1.25 ULN). A single repeat test is allowed during the Screening period to verify a result.
33. INR ≥Grade 2 (≥1.5 ULN). A single repeat test is allowed during the Screening period to verify a result.
34. Absolute Neutrophil Count (ANC) ≥Grade 2 (ANC ≤799 cells/mm^3). A single repeat test is allowed during the Screening period to verify a result.

35. The participant has a tattoo or other dermatological condition overlying potential injection sites which may interfere with interpretation of injection site reactions or administration of GSK3810109A.

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

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.3.1. Meals and Dietary Restrictions

- No dietary restrictions are required.

5.3.2. Caffeine and Alcohol

- There are no study-related restrictions on caffeine. Alcohol should be avoided for 24 hours prior to dosing of GSK3810109A and for 24 hours prior to all scheduled study visits until the initiation of standard of care cART (SOC Initiation Visit).

5.3.3. Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time. Rescreened participants should be assigned a new participant number for re-screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), intended to be administered to a study participant according to the study protocol. In this study, GSK3810109A is an experimental treatment for HIV-1 infected adults.

GSK3810109A is a recombinant human IgG1 antibody which is expressed as a soluble glycoprotein secreted from a recombinant Chinese Hamster Ovary (CHO) DG44 cell line.

GSK3810109A is targeted against the CD4 binding site of the HIV gp120 envelope protein.

6.1. Study Intervention(s) Administered

GSK3810109A Injection, 600 mg/6mL is a solution for infusion or injection. It is supplied as a sterile aqueous solution manufactured from bulk drug substance containing a target of 100 mg/mL of GSK3810109A, 10 mM sodium citrate/citric acid, 50 mM sodium chloride, 150 mM arginine-HCl, and 0.002% polysorbate-80 at pH 6.5. GSK3810109A Injection, 600mg/6mL contains a fill volume of 6.25 mL (6.00 mL withdrawable volume) of solution filled into a 10-mL glass vial with a 13-mm fluorinated-polymer coated chlorobutyl rubber stopper and a 13 mm blue flip-off overseal.

Table 2 Study Interventions

ARM	Dose groups and cohorts within Part 1 and Part 2
Intervention Name	GSK3810109A
Type	Biologic
Dose Formulation	Solution for injection or infusion
Unit Dose Strength(s)	600 mg/6 mL
Dosage Level(s)	40 mg/kg, 280mg flat dose, other doses to be determined following Part 1
Route of Administration	IV infusion, SC injection
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in vial. Each vial will be labeled as required per country requirement.
[Current/Former Name(s) or Alias(es)]	N6LS, N6LS bnAb (broadly neutralizing antibody), VRC-HIVMAB091-00-AB

6.2. Handling, Storage and Accountability of GSK3810109A

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Procedures Manual.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to

avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Pharmacy Procedures

Refer to the IB for further information on GSK3810109A.

Study Product and Administration Regimen

GSK3810109A Injection, 600 mg/6 mL is a clear, slightly yellow solution for infusion or injection. It is supplied as a sterile aqueous solution manufactured from bulk drug substance containing a target of 100 mg/mL of GSK3810109A, 10 mM sodium citrate/citric acid, 50 mM sodium chloride, 150 mM arginine-HCl, and 0.002% polysorbate-80 at pH 6.5. GSK3810109A Injection, 600mg/6mL contains a fill volume of 6.25 mL (6.00 mL withdrawable volume) of solution filled into a 10-mL glass vial with a 13-mm fluorinated-polymer coated chlorobutyl rubber stopper and a 13 mm blue flip-off overseal.

In calculating the dose to administer and number of vials to thaw, it should be assumed that the concentration is 100 mg/mL and that a volume of 6 mL can be withdrawn from a vial. For example, participants in Part 1, Group 1 will receive a dose of 40 mg/kg via IV route. Since each product vial contains at least 6 mL of 100mg/mL GSK3810109A, 4 vials will be required for the dose preparation for participants up to 60kg. For participants with body weight >60 kg to ≤75kg, 5 vials will be required; for participants >75kg to ≤90kg, 6 vials will be required; for participants >90kg to ≤105kg, 7 vials will be required and for participants >105kg to ≤115kg, 8 vials will be required.

Preparation of GSK3810109A for IV administration will require a 100 mL bag of 0.9% sodium chloride, United States Pharmacopeia (USP) (normal saline) and the correct dose of GS3810109A, as described in the IB. Preparation of GSK3810109A for SC administration will not require any diluent.

GSK3810109A Vialed Product

The product label designates the long-term storage temperature as -35°C to -15°C. Clinical site storage in a qualified, continuously monitored, temperature-controlled freezer.

Following thaw, GSK3810109A vials may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. Product may not be stored in direct sunlight. If stored at 2-8°C, vials must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 60 minutes and may be held at room temperature for up to 8 hours prior to product preparation.

Temperature Excursions

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance for the storage device to the study team. The affected product must be quarantined in a separate area. If the excursion results in thawed GSK3810109A material, DO NOT REFREEZE; store the thawed, vialed material at 2°C to 8°C.

- Provide the following information regarding the excursion: lot number, fill volume and number of vials affected; temperature range and length of excursion, including data log reports; handling of materials post excursion (e.g. transfer to alternate storage, including times); visual inspection data of the materials (e.g. did the materials appear to have remained frozen, were vials cracked, etc.). The study team will notify the site pharmacist if continued clinical use of the product is acceptable.

6.4. Preparation of Study Product Administration

This section describes how the site pharmacist will prepare the study product for administration and how the clinician will administer the product.

GSK3810109A is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C.

The following instructions apply to thawing GSK3810109A:

1. Thaw vial(s) for a minimum of 1.5 hours at controlled room temperature (maximum 27°C) after removing from the freezer.

2. Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described above in GSK3810109A Vialed Product.

3. Prior to preparation for administration, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles yet avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage. If the particles dissolve within the maximum storage times described in Section 6.3, the vials may be used for product preparation. **If particles continue to be observed, do not use the vialed product for SC or IV administration**. Refrigerated product must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 60 minutes before preparation and must be used within 8 hours of any subsequent return to room temperature.

4. If the thawed material is not administered within 24 hours of thaw, follow the storage information provided above in GSK3810109A Vialed Product.

Preparation is to be done using aseptic technique, in a laminar flow biosafety cabinet. Assure that only the required vials are present in the preparation unit during dilution, and medication labels are strictly segregated to avoid mix-ups. More information on product preparation can be found in the GSK3810109A Investigators Brochure (IB).

Preparation for IV Administration

For each IV infusion order, the participant's weight, dose level, and study group code will be included in the pharmacy order. To prepare an IV infusion, the pharmacist will: 1) fill an empty sterile bag with 100 mL of normal saline, 2) calculate the total milligrams of GSK3810109A needed, 3) retrieve the minimum number of thawed and particle free vials required to prepare the full dose, 4) withdraw the necessary amount of GSK3810109A, and 5) add this volume to the sterile bag using good pharmacy practices to maintain sterility. If commercially available, a pre-filled 100 mL bag of normal saline may also be used. Prior to preparation for administration, vials of GSK3810109A should be gently swirled for 30 seconds while avoiding foaming. DO NOT SHAKE THE VIAL.

An in-line filter infusion set must be used for IV product administrations and MUST comply with the following specifications: 1.2 micron PES (polyethersulfone) filter membrane, DEHP free, latex-free (equivalent to Braun #473994 filter extension set). When the in-line filter is added to the tubing, the administration set must then be primed. At the end of product administration, the IV administration set must be flushed with about 30 mL (or appropriate volume) of normal saline.

The study product solution will typically be administered IV over approximately 30 minutes using a volumetric pump. The total time needed to administer the dose may be longer based on factors such as participant tolerance. The rate of infusion may range from 10-20 mg/kg/hr at the lowest dose level to 80 - 160 mg/kg/hr at the highest dose level. The mL/hr infusion rate may vary based on the total volume needed to administer a full dose. An infusion time greater than 30 minutes is permitted.

Preparation for SC Administration

For each SC administration order, the participant's weight, dose level, and study group code will be included in the pharmacy order. To prepare a SC administration dose, the pharmacist will calculate the total mg needed and retrieve the minimum number of thawed, particle free vials needed to prepare the full dose. The maximum volume for SC injection is expected to be 2.5mL x 4 injections, but final dose will be determined following a review of data from Part 1. Prior to preparation for administration, vials should be gently swirled for 30 seconds avoiding foaming. **DO NOT SHAKE THE VIALS.** If particles are observed, follow instructions described in Section 6.4.

The needed volume of GSK3810109A must be withdrawn from the vial into 1 to 4 syringes (BD Luer-Lok 3 mL syringe; REF # 309657 or equivalent) using a 5-micron filter needle (BD Blunt Fill Needle – Filter, 18G 1 ½ inch; REF# 305211 or equivalent). A new filter needle must be used for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for SC injection at the time of administration.

The product may be administered by direct SC injection with needle and syringe. The clinician will use proper SC technique to ensure administration into SC fatty layer and a slow push to minimize discomfort or the excessive distention of overlying skin. The length of time to complete the infusion will vary depending on the dose given and participant tolerance of the infusion rate.

Handling of Prepared Product for IV or SC Administration

After product preparation in an IV bag, the prepared GSK3810109A may be stored at 18°C to 27°C for a maximum of 8 hours total including the infusion time. Product may not be stored in direct sunlight.

After preparation in syringes for SC administration, the prepared GSK3810109A may be stored at 2°C to 8°C up to 24 hours or at controlled room temperature (maximum 27°C) up to 4 hours. The product may not be stored in direct sunlight.

Study Product Disposition

The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with the institutional or pharmacy policy. Any unopened vials that remain at the end of the study will be returned to the production facility or discarded at the discretion of the sponsor in accordance with policies that apply to investigational agents. Partially used vials will not be administered to other participants or used for in vitro experimental studies. These vials will be disposed of in accordance with institutional or pharmacy policy.

6.5. Administration of GSK3810109A

All study product administrations will be completed according to the assigned group. For participants of childbearing potential, a negative pregnancy test must be obtained prior to product administration that day. Prior to product administration, temperature, blood pressure, heart rate (pulse) and weight will be recorded, and a targeted physical examination will be conducted. In all study groups, the participant will be observed for at least 2 hours following each product administration.

If a participant is assigned to an IV administration group, the IV access will be placed in an arm vein in an aseptic manner. A different site may be used for collection of PK blood samples; however, the same site may be used after flushing the line if another site is not available. GSK3810109A will be administered with approximately 100 mL of normal saline IV (as described in the IB) over approximately 30 minutes, with a target of 30 minutes for the initial infusion for each participant. Infusions lasting longer than 30 minutes are allowed. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

If a participant is assigned to a SC administration group, the SC administration site(s) to be used must be assessed as acceptable by the clinician and the participant. The preferred SC administration site is the abdomen, but the upper arm or thigh may be used. The SC dose will be administered by standard needle in a maximum volume of about 2.5 mL per injection site. Up to 4 SC injection sites may be used if deemed necessary by the clinician. SC administration sites should be at least 2 inches apart.

6.6. Measures to Minimize Bias: Randomization

Participants in both Part 1 and Part 2:

Open-label using central randomization via (IVRS/IWRS)	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the following steps: central randomization.

6.7. Study Intervention Compliance

- GSK3810109A will be intravenously or subcutaneously administered to participants at the site. Administration will be documented in the source documents and reported in the CRF.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit, after all laboratory tests have been drawn, and only when scheduled visits are ≥4 weeks apart. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment.

Clinical monitoring is recommended for participants taking methadone, as methadone maintenance therapy may need to be adjusted in some participants.

Non-protocol defined treatments or medical interventions (e.g., physical therapy, radiotherapy, surgical procedures) are permitted during the study for appropriate medical management of the participant.

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

6.8.1. Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered.
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to immunosuppressive effect; however, short treatment courses (e.g., 14 days or less) of oral prednisone/ prednisolone/ methylprednisolone are allowed. Topical, inhaled or intranasal use of glucocorticoids will be allowed.
- For participants with an **unanticipated** requirement for HCV therapy during study, interferon or any other medications that have a potential for adverse drug-drug interactions with study treatment are prohibited during the conduct of the study. Consult with the Medical Monitor in cases where concurrent HCV therapy is required.
- Acetaminophen (paracetamol) cannot be used in patients with acute viral hepatitis [James, 2009].

6.9. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule and number of groups, however the maximum dose will not exceed 40 mg/kg.

The decision to proceed to Part 2 will be made by the Safety and Dose Evaluation Committee and the study team based on viral load response (reduction in HIV-1 RNA). Additionally, safety, tolerability, and preliminary PK and/or pharmacodynamic data obtained in Part 1 will be used for dose selection in Part 2.

6.10. Intervention in Follow-Up Period: Combination Oral ART Standard of Care Phase

Participants who received GSK3810109A will continue to be followed for safety purposes according to the study schedule of activities. Initiation of standard of care, 2 or 3-drug integrase-based oral ART will start at the end of the last assessment day in the Monotherapy Phase in Part 1 and Part 2.

Participants will not be discontinued or replaced in the Long-Term Follow-Up period for initiating or changing ART. ART regimen changes will be documented in the participant's record.

Participants who remain viremic on their oral ARTs will be encouraged to talk to their primary care provider about their ART regimen, per Department of Human and Health Services [DHHS, 2019] guidelines or local regulations.

6.11. Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the poststudy care of the participant's medical condition, whether or not ViiV Healthcare/GSK is providing specific post-study treatment.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In Part 1 and Part 2 of the Monotherapy Phase, a single dose is administered, thus discontinuation of GSK3810109A is not applicable following the Day 1 IV infusion or SC injection.

During the SOC Follow-up oral combination ART phase, investigators will manage their participants per standard of care, following relevant guidelines [DHHS, 2019] or local guidance, except as outlined below for cases of virologic failure (Section 7.1.2). Sites should contact the Medical Monitor to discuss the management of individual participants on ART, whenever necessary.

Participants who received GSK3810109A, will continue to be followed for safety purposes according to the study schedule of activities (oral combination ART phase). Participants will not be discontinued or replaced in the study for initiating or changing ART. They will continue to be followed for safety purposes according to the study schedule of activities Section 1.3. ART regimen changes will be documented in the participant's record.

See the SOA, Section 1.3, for data to be collected at the time of study discontinuation.

Emerging safety data will be reviewed in stream as the study progresses and any participant meeting the following criteria will result in a study pause whilst a full safety review is conducted and the findings and recommendations presented to ViiV Safety and Labelling Committee (VSLC) for endorsement:

- Any Serious Adverse Event (SAE), regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator and Sponsor.
- Acute Allergic reaction or cytokine release syndrome (DAIDS criteria Grade 3-4) reasonably attributable to dosing with GSK3810109A, in the opinion of the Investigator and Sponsor.
- Any AE of Grade 4 intensity assessed as related to GSK3810109A, as reported by the Investigator.

- Any participant meeting liver chemistry stopping criteria.
- Any participant meeting QTc stopping criteria.

Aggregate thresholds:

- If ≥30% of participants within a dose group have a Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride).
- Any pattern of poorly tolerable, or clinically significant adverse events observed within a dose group are consistent across at least 50% of participants

Relevant reporting and discussion with the Medical Monitor, relevant study team personnel, and the IRB/IEC will take place before resumption of dosing. Every effort will be made to take a blood sample at the time of the AE for PK analysis.

7.1.1. QTc Stopping Criteria

QTc stopping criteria is defined as a participant who has a QTc interval >550 msec considered causally related to IP. The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5 to 10 minute) recording period.

When performing ECGs, the same QT correction formula 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.

For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.

Once the QT correction formula has been chosen for a participant's eligibility, the same formula must continue to be used for that participant for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.

If a participant meets QTc stopping criteria, the participant will remain in the study to be evaluated for all the follow up per the SoA or until GSK3810109A is undetectable for appropriate procedures, including blood plasma PK sampling, and safety evaluations. The participant will not be removed from the study for medical reasons, unless they withdraw consent to continue participation.

7.1.2. Virologic Failure

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure during the SOC follow up period.

7.1.3. Definition of Protocol-Defined Virologic Failure

For the purposes of clinical management in this study, the criteria detailed below will apply during the SOC Follow-up period of the study. The virologic failure definition does not apply during Part 1/ Part 2.

Suspected Virologic Failure: A single HIV-1 RNA value as defined by Virologic Nonresponse or Virologic Rebound.

Confirmed Virologic Failure: Any of the below conditions are met once the Investigator has confirmed participant compliance:

Virologic Non-Response Criteria:

A decrease in plasma HIV-1 RNA from the SOC Initiation Visit (end of Monotherapy Phase) of less than 2.0 log10 c/mL at SOC Follow-up Week 8, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL,

Confirmed plasma HIV-1 RNA ≥200c/mL on or after SOC Follow-up Week 12.

Virologic Rebound Criteria:

Confirmed rebound in plasma HIV-1 RNA ≥200c/mL after prior suppression to <200c/mL.

Confirmatory testing of virologic non-response:

The participant should have received full doses of ART treatment for at least two weeks at the time confirmatory plasma HIV-1 RNA is conducted, if possible. The current ART regimen should continue to be administered and no additional ART should be added during re-testing.

Upon notification that a participant's HIV-1 RNA plasma level initially meets one of the above criteria, the investigator should query the participant regarding intercurrent illness, recent immunization, interruption of therapy or inadequate adherence.

All cases meeting "virologic management" criterion must be confirmed by a second measurement performed at least two weeks but not more than 4 weeks apart from the date of the original sample, unless delay is necessary to meet the requirements of confirmatory HIV-1 RNA testing as outlined below.

The following guidelines should be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

Confirmatory testing should be scheduled at least two weeks but not more than 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all antiretrovirals in the regimen.

Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the participant should receive full dose of all antiretrovirals in the regimen.

If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2-4 weeks following resumption of full dose of all antiretrovirals in the regimen.

The participant should have received full doses of HAART for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done.

Sites should contact the Medical Monitor to discuss individual participants, whenever necessary.

7.1.4. Managing Virologic Failure

Once a participant has been determined as meeting a protocol defined confirmed virologic failure criterion, a plasma sample from the suspected virologic failure time point will be sent for reverse transcriptase (RT)/ protease (PRO)/ integrase (IN) genotypic and phenotypic HIV-1 resistance testing and the result made known to the study investigator when available to advise on a new ARV-regimen. Plasma samples from storage will also be obtained at unscheduled visits including the time of Confirmed Virologic Failure criteria.

Plasma HIV-1 RNA values determined by the central laboratory only will be used to assess virologic management criteria. Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as meeting a virologic failure criterion, the investigator should query the participant regarding intercurrent illness, recent immunization, adherence, or interruption of therapy.

Participants may continue to receive their SOC regimen at the discretion of the investigator until results of HIV-1 resistance testing are available. Based on the results of the resistance testing, the ART regimen may be modified by the investigator.

A participant who meets virologic failure may remain in the study.

Selection of ART regimen for participants meeting confirmed virologic failure criteria will be recorded in the eCRF.

The protease RT/PRO/IN genotypic and phenotypic assays used in this study are not validated for plasma HIV-1 RNA levels <500 c/mL. Nevertheless, for all participants who meet confirmed virologic failure criteria, plasma samples will be analyzed in an attempt to obtain genotype/phenotype data on samples with HIV-1 RNA ≥200 c/mL, as possible.

For participants meeting confirmed virologic failure, "Meeting Confirmed Virologic Failure" will be recorded in the eCRF as reason for the modification to a new ART-regimen.

7.2. Liver Chemistry Stopping Criteria

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

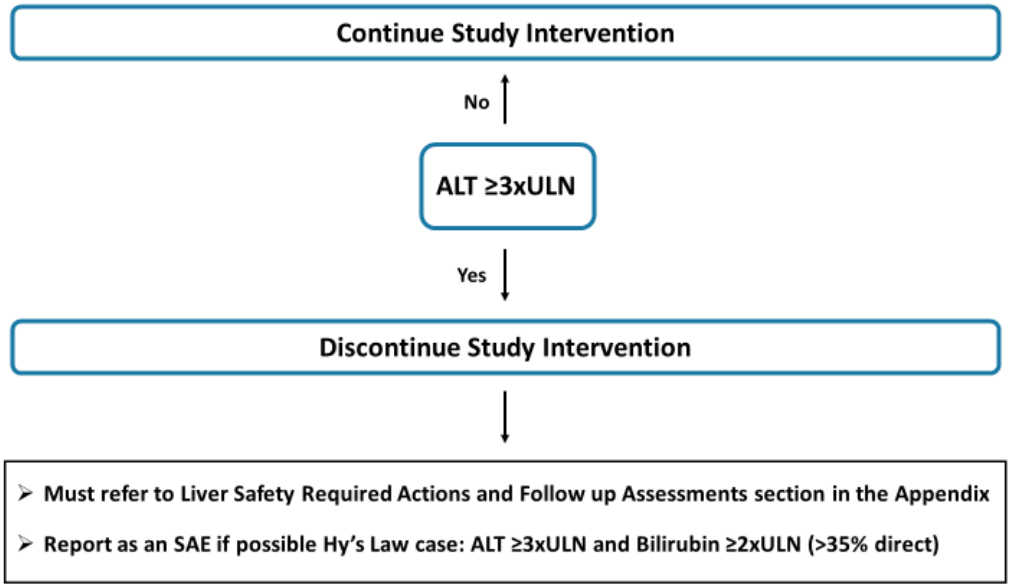
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

In the monotherapy phase of Part 1 and Part 2, discontinuation of GSK3810109A is not possible for abnormal liver tests as this is a single-dose study. The expected duration of systemic exposure to GSK3810109A is 6 to 9 months. If a participant meets liver chemistry stopping criteria, the study will pause to conduct an evaluation of the relevant safety data. The findings and recommendations on dosing resumption will be presented to VSLC for endorsement.

Discontinuation of ART in the Long-Term Follow-Up period for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Section 10.7.
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes ART discontinuation and initiating a new ART is in the best interest of the participant.

Figure 1 Phase 2a Liver Chemistry Stopping – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; SAE = serious adverse event; ULN = upper limit of normal

Refer to Appendix 7 for required Liver Safety Actions and Follow up Assessments.

ART Restart:

If participant meets liver chemistry stopping criteria, do not restart or rechallenge the participant with the ART in the Long-Term Follow-Up period unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**,
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the participant.
- Refer to Section 10.7 for full guidance.

If GSK/ViiV Medical Governance approval to restart/re-challenge participant with ART **is not granted**, then participant must discontinue their ART and initiate an alternate ART and may continue in the study with alternate ART interventions.

7.2.1. Temporary Discontinuation

As GSK3810109A is a single dose administration in Part 1 and Part 2 of the Monotherapy Phase, a temporary withdrawal of study drug is not applicable.

Participants may have a temporary interruption to their oral ART in the long-term follow-up period for management of toxicities. Such interruption of ART does not require withdrawal from the study. However, consultation with the Medical Monitor is required. Start and stop dates of ART and reason for temporary interruption will be recorded in the eCRF.

7.3. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw consent and discontinue participation in this study at any time at his/her own request. The investigator may also, at his or her discretion, discontinue the participant from participating in this study at any time (e.g., safety, behavioral or administrative reasons). This is expected to be uncommon. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

- All participants who discontinue prematurely from the study will be asked for additional information to establish the reason for withdrawal. Participants are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the Completion/Withdrawal section of the electronic case report form (eCRF). Every effort should be made by the investigator to follow-up participants who withdraw from the study.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA, Section 1.3 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- An in-clinic withdrawal visit will also be used to assess participants with ongoing AEs, and serious adverse events (SAEs) related & not related to study drug and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant.

7.4. 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA, Section 1.3.

Visits for participants in the monotherapy phase should occur as projected according to the Day 1 visit. However, in order to facilitate scheduling around weekends and holidays, the following visit windows have been stipulated:

Table 3 Visit Windows

Day 1, 3 Hour	3 hours (±30 minutes) from the start of infusion or time of injection(s)
Day 1, 24 Hours	24 hours (±2 hours) from the start of infusion or time of injection(s)
Day 3	2 calendar days after Day 1
Day 6	5 calendar days (±1 day) after Day 1
Day 9	8 calendar days (±2 days) after Day 1 and at least one calendar day after the Day 6 visit
Day 11	10 calendar days (±2 days) after Day 1 and at least one calendar day after the Day 9 visit
Day 14	13 calendar days (±2 days) after Day 1 and at least one calendar day after the Day 11 visit
Day 17	16 calendar days (±2 days) after Day 1 and at least one calendar day after the Day 14 visit
Day 21	20 calendar days (±2 days) after Day 1 and at least one calendar day after the Day 17 visit
Every 7 days while remaining in the monotherapy phase	Target date (±3 days) calculated from Day 1
SOC Initiation Visit	No visit window- this visit will be conducted either in place of a scheduled visit or as an unscheduled visit upon confirmation that a monotherapy endpoint has been reached.
SOC Follow-up +1 Week	1 week (±3 days) after the SOC Initiation Visit
SOC Follow-up +4 Weeks	4 weeks (±7 days) after the SOC Initiation Visit
SOC Follow-up +8 Weeks	8 weeks (±7 days) after the SOC Initiation Visit
SOC Follow-up +16 Weeks	16 weeks (±7 days) after the SOC Initiation Visit
SOC Follow-up +24 Weeks	24 weeks (±7 days) after the SOC Initiation Visit
SOC Follow-up +32 Weeks	32 weeks (±7 days) after the SOC Initiation Visit
SOC Follow-up +48 Weeks	48 weeks (±7 days) after the SOC Initiation Visit

There are visit windows in the SOC follow-up phase from the projected visit dates. However, the number of tablets dispensed should be considered when scheduling the next visit to assure continuity of cART until the next scheduled visit

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
    - The maximum amount of blood collected from each participant (weighing 50 - 115kg) will not exceed approximately 500 ml over a 2-week period during the Monotherapy Phase.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples such that they are not viable for assessment.

- **Screening Assessments:**

All participants will be screened for eligibility before being randomized, preferably within 28 days of the Screening visit. Randomization on Day 1 may occur as soon as all Screening procedures have been completed and results are available and on file. The 28-day screening period may be extended (i.e., up to 35 days) to allow receipt of all Screening assessment results and to accommodate scheduling.

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

- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).

- Protocol waivers or exemptions are not allowed.

- **Day 1 Assessments**

On Day 1, the following assessments must be completed prior to dosing: confirm participant meets all inclusion and exclusion criteria, vital signs, weight, temperature, and laboratory assessments.

For all assessments on Day 1, see the Day 1 SoA in Section 1.3.2. See Section 6 for preparation and administration of GSK3810109A.

Part 1 of the study will evaluate two doses of GSK3810109A administered by IV infusion on Day 1 in the 2 groups. Enrollment in Part 1 will continue until approximately 10 evaluable participants are confirmed in Group 1 to support the Go / No Go criteria (see Section 4.4 and Section 9.5). Participants will be randomized equally (1:1) between Group 1 and 2.

- Part 1 Group 1 (high dose group) will assess a 40 mg/kg IV infusion of GSK3810109A.

- Part 1 Group 2 will assess GSK3810109A administered at a reduced flat dose (280 mg) IV infusion.

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Following completion of a pre-defined informal interim analysis of data from Part 1 and according to criteria defined in Section 4.4 and Section 9.5, further groups of approximately 10 participants will then be studied in Part 2 across a range of dose

infusion levels (depending upon the data obtained in Part 1), and a dose administered subcutaneously. Participants will be randomized equally between all groups in Part 2.

The exact doses in Part 2 will be defined based on data from Part 1.

As in Part 1, after the infusion or SC injection in Part 2, samples will be collected as per the SoA.

Standard of Care Long Term Follow-up Phase

For all assessments in the Standard of Care Follow-up Phase, see the SoA in Section 1.3.3.

All participants will initiate an oral integrase-based ART (dolutegravir + lamivudine regimens will be provided by the study; alternative integrase inhibitor-based regimens may be reimbursed after discussion and agreement with the Medical Monitor) after monotherapy phase on the day of the SOC Initiation Visit. PK-enhancing agents will not be counted as part of the ART regimen.

Participants who remain viremic on antiretroviral therapies (ARTs) will be encouraged to talk to their primary care provider about their ART regimen, per Department of Human and Health Services (DHHS, 2019) guidelines or other local regulations.

Participants who receive the study product will continue to be followed for safety purposes according to the study schedule of evaluations. Participants will not be discontinued or replaced in the study for initiating or changing ARTs. They will continue to be followed for safety purposes according to the study schedule of evaluations. ART regimen changes will be documented in the participant's record.

8.1. Efficacy Assessments

8.1.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Schedule of Activities (Section 1.3). Methods to be used may include but are not limited to the Abbott Realtime HIV-1 Assay lower limit of quantitation 40 c/mL. In some cases, (e.g., where the plasma HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

8.1.2. Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ and CD8+ lymphocyte counts, CD4+/CD8+ ratio) according to the Schedule of Activities (Section 1.3).

8.1.3. Pharmacokinetics

GSK3810109A serum levels will be evaluated per the schedule in the SoA. See Section 8.5 for details.

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8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal, bone, and neurologic disorders will be collected.
- Height and weight will also be measured and recorded. Shoes should be removed for height and weight measurements.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest in a quiet setting without distractions (e.g., television, cell phones) and will include temperature, systolic and diastolic blood pressure, and pulse. Respiratory rate and SPO2 will also be measured during the in-clinic period on Day 1.

8.2.3. CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Schedule of Activities (Section 1.3.1). HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults [CDC, 2014]. When assessing CDC stage at Screening, consider only the latest available CD4+ T-cell count, except when the participant had an active Stage 3 event. Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

CDC Stage 1, 2 or 3 at enrolment → Death.

8.2.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The ECG should be read locally and be centrally archived. Please contact the Medical Monitor if any concerns.
- Refer to Section 7.1.1 for ECG management criteria and additional QTc readings that may be necessary.

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- For visits with fasting labs, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
- 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in the Study Reference Manual (SRM), must be conducted in accordance with the laboratory manual, through the central laboratory (Q2 Solutions), and the SoA (Section 1.3).

8.2.6. Immunogenicity Assessments

Anti-GSK3810109A antibodies (ADA) will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. Details

regarding sample collection, processing, storage, and shipment will be provided in the SRM or equivalent.

Serum samples will be tested using a tiered testing scheme (ie, screen, confirm, titer). First, all samples will be tested in the screening assays. Next, samples that screen positive will be tested in a confirmation assay to determine the specificity. Finally, samples that confirm positive will be titrated to quasi-quantitate the amount of anti-GSK3810109A antibodies in the sample. The results (e.g., positive or negative) and titer values will be reported. Other analyses may be performed to characterize the ADA further.

- The detection and characterization of antibodies to GSK3810109A will be performed using validated assays. Blood samples will also be collected and analyzed for GSK3810109A concentrations at the same time points as the immunogenicity samples to enable interpretation of the ADA data (SoA, Section 1.3).

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

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

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

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to GSK/ViiV Healthcare within 1 week of the investigator diagnosing a possible suicidality-related AE. Sites should have a plan in place for managing possible risks for suicide-related events.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3. As described in Appendix 3, intensity of AEs (and lab abnormalities) will be graded using the division of AIDS (DAIDS) Grading table.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

For Adverse Events related to COVID-19, please see Section 10.10.5.2.

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

- All SAEs will be collected from the start of study intervention until the last visit at the time points specified in the SoA (Section 1.3). 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 GSK product will be recorded from the time a participant consents to take part in the study.

- All AEs will be collected from the start of intervention until last study visit at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.5. 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 after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. 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 Section 10.3

- 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. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Section 10.3.4.

AEs of special interest include: injection site reactions, infusion related reactions, serious/severe immune reactions (including anaphylaxis and cytokine release syndrome).

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

8.3.5. Pregnancy

- Details of all pregnancies in female participants at birth will be collected after the start of study intervention and until completion of the long-term follow-up period.
- 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 Section 10.5.3

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections [Section 10.8] will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If either of the above conditions is met, then record the Disease Related Event on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly [Section 8.3.1] to GSK.

8.3.8. Specific Toxicities/Adverse Event Management

8.3.8.1. Injection/Infusion Site Reactions (ISRs)

Injection or infusion site reactions will be managed through investigator assessment throughout the study. All ISRs that are either serious, Grade 3 or higher, or persisting

beyond 2 weeks must be discussed with the Medical Monitor to determine etiology and assess appropriate continued study participation.

Digital photographs may be documented where possible on all participants who have an injection site reaction, with observable findings, that is either serious or Grade 3 or higher, or that persists beyond 2 weeks. Dermatology will be consulted on all participants who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

Details regarding photo collection and any other follow up will be given by the Medical Monitor at the time of assessment.

ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the participant's ability to perform activities of daily living. The required intervention should be documented on the appropriate eCRF page.

Diary Cards

Participants will complete a diary card following GSK3810109A infusion/injection. This allows participants to record and score the severity of any reactions, record the impact of the infusion/injection on normal daily activities as well as any action taken such as use of analgesic medication following the infusion/ injection.

Participants will be required to bring the original completed diary cards to the next clinic visit and hand over to the investigator/site staff who will enter the information from the ISR diary cards into the relevant ISR Diary section of the eCRF within the same timeframe as normal eCRF data entry (1 working week of the visit).

8.3.8.2. Severe Immune Reactions

Intravenous access will be placed in an arm vein in an aseptic manner. GSK3810109A will be administered with approximately 100 mL of normal saline IV over approximately 30 minutes. Infusions lasting longer than 30 minutes are allowed. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

Vital signs will be monitored during the infusion and prompt treatment of anaphylaxis is critical, with subcutaneous or intramuscular epinephrine and intravenous fluids. Adjunctive measures include airway protection, antihistamines, steroids, and beta agonists. Some symptoms may be treated by slowing or stopping the infusion. Supportive treatment may also be indicated for some signs and symptoms. Medication administered during anaphylactic reaction will be recorded in CRF.

Patients with anaphylaxis should be closely monitored for the possibility of recurrent symptoms after initial resolution. Urinary and serum histamine levels and plasma tryptase levels drawn after onset of symptoms may assist in diagnosis.

8.4. Treatment of Overdose

For this study, any dose of GSK3810109A greater than 40 mg/kg within a 2 week period will be considered an overdose.

The Investigator should use clinical judgement in treating overdose, as ViiV Healthcare is unable to recommend specific treatment other than supportive care.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Monitor vital signs regularly for several hours after the overdose
3. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3810109A can no longer be detected systemically.
4. Obtain a serum sample for PK analysis from the date of the overdose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
5. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Since this is a single dose administration of GSK3810109A, there will be no dose interruptions or modifications.

8.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of serum concentrations of GSK3810109A at the time points specified in the SoA (Section 1.3). The timing of PK samples may be altered and/or PK samples may be obtained at additional time points during the study to ensure thorough PK monitoring 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.
  - Samples will be used to evaluate the systemic PK of GSK3810109A. Each serum sample will be collected equally into 2 aliquots with one aliquot as a backup to be stored at sites and shipped later. Samples collected for analyses of GSK3810109A serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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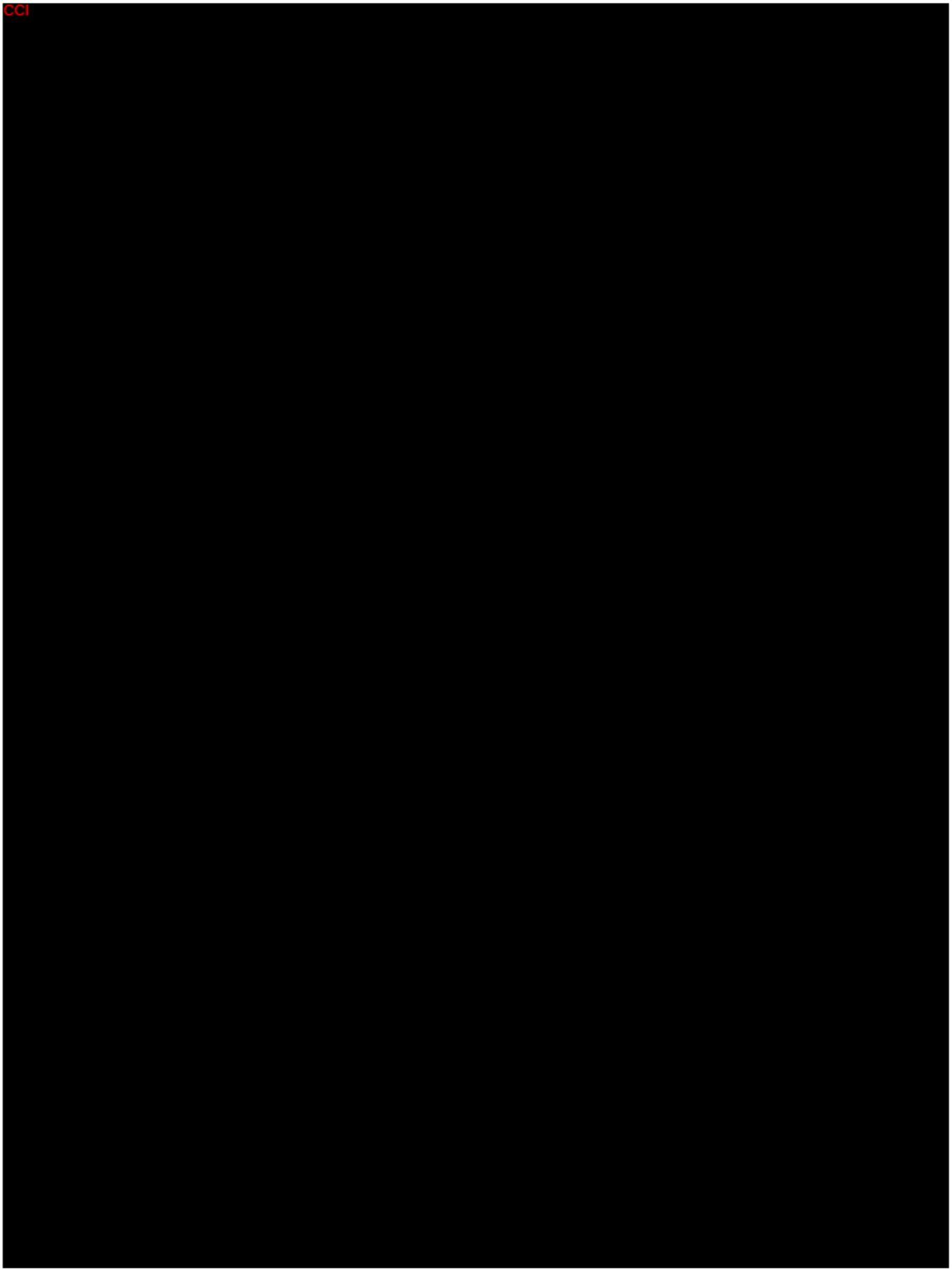

Phenotypic and functional properties of T cells will be investigated by analyzing cytokine secretion in response to HIV antigens before and at several timepoints post antibody infusion.

8.7.3. B-cell Responses

Whole venous blood samples will be obtained from each participant according to the Schedule of Activities in Section 1.3. Details concerning the handling, labeling and shipping of these samples will be supplied separately.

Phenotypic and functional properties of B cells will be investigated by measuring the heterologous neutralization profile before antibody infusion and at the SOC Follow-Up Week 48 timepoint. The heterologous neutralization profile analysis may be carried out by Monogram Biosciences.

8.8. Viral Genotyping and Phenotyping

At Screening, samples will be collected for HIV-1 RT/PRO/IN genotype and phenotype. Results will be provided to the Investigator to assist in the selection of the standard of care regimen that will be initiated at the end of Part 1 and Part 2. Results will also be made available for screened participants who do not meet other eligibility for study inclusion in order to inform initial HIV treatment plans outside of study. Resistance test data should be reviewed as soon as available. If oral ART has been initiated prior to results becoming available, investigator should determine if a participant's regimen should be modified.

During the SOC Follow-Up, participants experiencing confirmed virologic failure will have plasma samples tested for HIV-1 RT/PRO/IN genotype and phenotype from samples collected at the time of suspected virologic failure; these results will be reported to the Investigator as soon as available to provide guidance for election of a switch regimen.

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense testing methods for protease (PRO) and reverse transcriptase (RT), or with their GeneSeq Integrase and PhenoSense Integrase assays.

CCI

[redacted]

CCI

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested, and study conclusions will be based on estimation. The primary treatment effect to be estimated is the maximum plasma HIV-1 RNA decline from baseline over the Monotherapy Phase for each dose level and method of administration (intravenous or subcutaneous).

9.2. Sample Size Determination

An estimated 50 participants will be randomly assigned to GSK3810109A across approximately 5 groups to achieve approximately 10 evaluable participants for each group.

The sample size of approximately 10 evaluable participants for Group 1 was chosen to allow for an accurate estimate of the primary treatment effect of the highest dose. A sample size of approximately 10 for the remaining groups was chosen primarily based on

feasibility in order to explore approximately 4 additional groups at varying dose concentrations and modes of delivery (IV and subcutaneous). The required sample size of approximately 10 for Group 1 is to be able to account for the possibility of some participants being non-sensitive to GSK3810109A, and to accurately estimate the primary treatment effect among the sensitive-only subgroup.

Based on viral load decline data from 3 previous POC studies with bNAbs (VRC01: [Lynch, 2015]; 10-1074: [Caskey, 2017]; 3BNC117: [Caskey, 2015]), we assumed a target value viral load decline (VLD) for individual participants from the highest dose (Group 1) to be 1.3 $\log_{10}$ when analysing all participants regardless of their sensitivity to GSK3810109A. We also assumed a minimum value of 1 $\log_{10}$ VLD to represent a clinically meaningful change. Alternatively, a target value of 1.4 $\log_{10}$ VLD among participants sensitive to GSK3810109A represents a meaningful decline to proceed with the study. In the absence of sensitivity data during the study we use a $\geq$0.5 $\log_{10}$ decrease as a proxy for sensitivity for our interim analysis. We used these thresholds in our interim Go/No Go criteria, detailed in Section 9.5 and powered the study to make a decision on whether to proceed to Part 2 based on the VLD observed in Part 1 among the high-dose group (Group 1).

To determine the operating characteristics of the interim decision and inform our sample size, we simulated trial data as arising from a mixture of 2 normal distributions to describe the VLD among a population consisting of both sensitive and non-sensitive individuals. The mixing parameter is the proportion of non-sensitive individuals in the population and the mean VLD varying for sensitive individuals and 0.2 for non-sensitive individuals, both with SD=0.4. We simulated data with mixing parameters of 0.10 or 0.30 and mean VLD for sensitive individuals ranging from 0.2 to 2 as listed in Table 4.

We simulated 10,000 trials for each unique combination of the above parameter values. For each unique scenario, we calculated the proportion of trials with Go, No-Go, and Consider for the informal interim analysis described in Section 9.5. These proportions estimate the probabilities of each decision and are shown below in Table 4.

Table 4 Probability Decision at Interim Based on a Sample Size of 10

% non-sensitive participants in population	True VLD for sensitive participants in population	Probability of Decision at Interim		
		Go	No-Go	Consider
	0.2: No treatment effect	0.0%	99.8%	0.2%
10%	1.1	24.1%	61.7%	14.2%
	1.25	58.0%	26.3%	15.7%
	1.4	83.0%	7.5%	9.5%
	2	96.3%	0.0%	3.7%
30%	1.1	5.4%	87.4%	7.2%
	1.25	19.0%	64.4%	16.7%
	1.4	35.1%	37.3%	27.6%
	2	57.5%	0.6%	41.9%

To assess the sensitivity of the above analysis to the sample size and parameter assumptions we assessed the operating characteristics under the following 4 scenarios:

1. There is no effect on VLD (mean VLD=0 for entire population).
2. GSK3810109A has mean VLD of 1.4 among sensitive population, but 50% of the population is non-sensitive to GSK3810109A.
3. GSK3810109A has mean VLD of 1.4 among sensitive population and only 10% of the population is non-sensitive to GSK3810109A.
4. GSK3810109A has mean VLD of 1.4 among the entire population (i.e. entire population is sensitive to GSK3810109A).

For each scenario we calculated the operating characteristics above for sample sizes of 8, 10, 20, and 50 to see how sensitive the operating characteristics are to sample size. The results are shown in Table 5.

Table 5 Sensitivity to Sample Size and Parameter Assumptions

Scenario	N	Prob. Go	Prob. No Go	Prob. Consider
Treatment doesn't work VLD=0 for all	8	0.0%	99.8%	0.2%
	10	0.0%	99.8%	0.2%
	20	0.0%	99.9%	0.1%
	50	0.0%	100.0%	0.0%
Treatment works well for sensitive participants and 50% non-sensitive (sensitive VLD=1.4 and non-sensitive VLD=0.2)	8	9.3%	58.3%	32.4%
	10	7.1%	65.8%	27.1%
	20	2.6%	79.8%	17.7%
	50	0.0%	91.1%	8.9%
Treatment works well for sensitive participants and 10% non-sensitive (sensitive VLD=1.4 and non-sensitive VLD=0.2)	8	80.7%	6.5%	12.8%
	10	83.0%	7.5%	9.5%
	20	89.4%	4.1%	6.5%
	50	87.1%	0.2%	12.8%
Treatment works well and all participants sensitive (sensitive VLD=1.4)	8	97.6%	0.7%	1.7%
	10	97.9%	0.4%	1.7%
	20	99.2%	0.0%	0.9%
	50	99.9%	0.0%	0.1%

The false positive rates (Prob. Go in scenarios 1 and 2) and false negative rates (scenarios 3 and 4 Prob. No Go) are well controlled <10% across all sample sizes tested. Additionally, an increase in sample size under scenario 3 does not drastically improve power (Prob. Go). Therefore, a sample size of approximately 10 for Group 1 is sufficient for this analysis.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomized to.
Safety	• All participants who received at least one dose of study treatment. • This population will be based on the treatment the participant actually received. **Note: Participants who were not randomized but received at least one dose of study treatment should be listed.**
Full Analysis Set (FAS)	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant was randomized to. **Any participant who receives a treatment randomization number will be considered to have been randomized.**
Per-Protocol (PP)	• All participants in the FAS population who comply with the protocol. • Protocol deviations that would exclude participants from the PP population will be defined in the Reporting and Analysis Plan.
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).**

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

Plasma HIV-1 RNA values will be used for the efficacy analysis based on the FAS population (and the PP population if it differs from FAS). Change from baseline in plasma HIV-1 RNA will be calculated for each participant on each assessment visit of the trial. Maximum change from baseline during the monotherapy period will also be calculated for each evaluable participant. A randomized participant is considered evaluable if plasma HIV-1 RNA measurements are available at baseline and at least 3 out of the 4 scheduled monotherapy timepoints from Day 3 through Day 11 inclusive. Based on Part 1 data, the definition of evaluable for Part 2 may be changed. In this case, the definition of evaluable for Part 2 will be updated in the statistical analysis plan.

Maximum change in plasma HIV-1 RNA from baseline among evaluable participants will be summarized by treatment. Change in plasma HIV-1 RNA from baseline will be summarized by treatment at each visit/assessment.

Plasma HIV-1 RNA will be listed by treatment, participant, and time point and summarized by treatment and time point along with change from baseline.

Change in CD4+ T cell counts will be summarized by treatment, over time.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population. Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library. No formal statistical analysis of the safety data will be conducted.

9.4.2.1. Immunogenicity Analyses

For each participant, the results and titers of ADA will be listed for each assessment time point, along with the time-matched drug concentration. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant by dose group. Additional analyses may be conducted as appropriate to the data. Information detailing the analyses will be included in the statistical analysis plan.

9.4.2.2. Pharmacokinetic Analyses

The single dose systemic exposure of GSK3810109A will be estimated over the monotherapy duration. Relevant PK parameters such AUC, Cmax and Tmax will be summarized based on available data. The systemic drug concentrations may subsequently be utilized for a PK/PD analysis to characterize the exposure-response relationship between GSK3810109A exposure and viral load decline.

9.4.3. Other Analyses

Pharmacokinetic, pharmacodynamic, virology, and biomarker analyses will be described in the statistical analysis plan. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

Additionally, special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the main study statistical analysis plan (SAP); alternatively, a separate SAP focusing on modified data handling rules (eg, changes to analysis populations, visit windows and endpoints) and analyses (eg, sensitivity analyses to assess impact of and account for missing data) may be prepared, taking in to account applicable regulatory guidance and industry best practices for handling such situations.

9.5. Interim Analyses

An informal interim analysis of preliminary antiviral activity will occur after the earlier of the Day 21 visit or end of monotherapy of the last high-dose (Group 1) participant. Antiviral activity will be measured by maximum viral load decline (VLD) from baseline

during monotherapy (Part 1) in evaluable participants in the high dose group (Group 1). This analysis will decide Go/No Go based on emerging evidence of efficacy. The Safety and Dose Evaluation Committee (SDEC) will also consider emerging safety data from both dosing groups before deciding whether to proceed with Part 2 of the trial.

The subgroup for the efficacy Go/No Go decision as well as the criteria used will depend on the proportion of evaluable participants who are non-responders, defined as those participants with a maximum VLD less than 0.5 $\log_{10}$. If less than 30% of evaluable participants are non-responders, then the analysis will be based on all evaluable participants in Group 1 (Scenario 1) from the FAS population. If 30% or more of participants are non-responders, then the analysis will include only those participants in Group 1 from the FAS population with a VLD of at least 0.5 $\log_{10}$ (Scenario 2).

For this analysis, the Bayesian posterior probabilities of the mean maximum $\log_{10}$ VLD (based on the Group 1 data used in each scenario) exceeding/not exceeding certain thresholds will be calculated. For the Bayesian calculation, we assume the maximum VLD follows a normal distribution (mean, standard deviation) and the assumed priors are taken to be non-informative, with Normal (0, 100) for mean and Inverse Gamma (0.01, 0.01) for standard deviation. The following decision criteria will be used:

Scenario 1 (< 30% of evaluable participants are non-responders):

If Prob. (maximum $\log_{10}$ VLD >1) ≥70% AND Prob. (maximum $\log_{10}$ VLD>1.3) ≥ 10%, the trial will proceed (GO).

If Prob. (maximum $\log_{10}$ VLD>1) <70% AND Prob. (maximum $\log_{10}$ VLD>1.3) <10%, the trial will not proceed (STOP).

Otherwise, the study team will consider the whole preliminary clinical data (e.g. safety, tolerability and PK, as available) and decide whether to proceed (CONSIDER).

Scenario 2 (>=30% of evaluable participants are non-responders):

If Prob. (maximum $\log_{10}$ VLD <1.4) >50%, the trial will not proceed (STOP).

Otherwise, the study team will consider the whole preliminary clinical data and decide whether to proceed (CONSIDER). In this scenario the team will also determine whether to include a pre-screen for GSK3810109A sensitivity if the decision is to proceed with the trial.

If the decision based on Group 1 data is to proceed with the trial, then the antiviral activity of both Group 1 and Group 2 will be reviewed to aid dose selection and mode of administration of monotherapy for the subsequent groups in Part 2.

At the Part 1 interim analysis stage, safety Go / No-Go criteria from the Safety Population are pre-defined as:

No Go:

- If ≥35% of treated participants in Part 1 receiving GSK3810109A have a clinically significant Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) determined by the SDEC

Go:

- The above safety 'no go' criteria is not met.

The safety interim analysis will be based on all available safety data from the monotherapy phase of Part 1 participants at the time of the interim efficacy data cut-off. >65% of Part 1 participants must complete monotherapy without a clinically significant Grade 3 or lab abnormality trend before the study can proceed with Part 2 (Go decision). Additional ongoing safety data from Part 1 participants until their monotherapy completion will be added to the interim safety analysis until a definitive decision (Go or No Go) can be reached.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Consideration

- This study will be conducted in accordance with the protocol and with:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

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

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

GSK/ViiV Healthcare (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3810109A or about HIV; publish the results of these research efforts; work with governmental agencies or insurers to have GSK3810109A approved for medical use or approved for payment coverage.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

10.1.5. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor

before submission. This allows the sponsor to protect proprietary information and to provide comments.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6. Dissemination of Clinical Study Data

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

ViiV Healthcare/ GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

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 ViiV Healthcare/ GSK Policy.

ViiV Healthcare/ 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.

10.1.7. 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. This includes accurate and timely transcription of the data recorded on the participant-completed ISR Diary cards into the relevant section of the study eCRF.
- Guidance on completion of CRFs will be provided in the Study Reference Manual.
- Quality tolerance limits (QTLs) will be pre-defined in the quality tolerance limits plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

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

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. This includes the participant-completed ISR Diary cards (source documents) and the data transcribed from the dairy cards into the eCRF. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Monitoring Plan.

10.1.9. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

10.1.10. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

- Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins.
- 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.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy Testing: Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 6 Protocol-Required Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
MCH		%Reticulocytes	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Calcium			
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA			
HIV-1 genotype/phenotype (RT/PRO/INI)			
CCI [redacted]			
CD4+ and CD8+ cell counts [CD4/CD8 ratio]			
Peripheral Blood Mononuclear Cells (PBMCs)			
Hepatitis B (HBsAg), anti-HBc, anti-HBsAg, and hepatitis C antibody[e]			
Syphilis serology + Reflex Rapid Plasma Reagin (RPR)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)			
Pregnancy test for women of childbearing potential[f]			
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate			
Genetics Sample			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			
ntibodies (ADA)			
CCI [redacted]			
GSK3810109A PK analysis			
COVID-19 PCR or antigen testing			
CCI [redacted]			

AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HBsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 ×ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) HBV DNA will only be performed for participants with a positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).
f) Urine pregnancy test/ serum pregnancy test will be performed according to the SoA (Section 1.3).
g) The intention is to utilize these biomarker data for research purposes; the sponsor will not be reporting real-time results of these assessments to the investigator

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless

judged by the investigator to be more severe than expected for the participant's condition.

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

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
o Results in death o 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 or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) 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.
Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy

- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information 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.
- Participant-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

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

10.3.5. Reporting of SAE to GSK

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 at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

10.4. Appendix 4: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales [DHHS, 2019]. Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 8.3.

Monotherapy Phase

In Part 1 and Part 2 of the Monotherapy Phase, a single dose is administered, thus discontinuation of GSK3810109A is not applicable following the Day 1 IV infusion or SC injection. Participants who received GSK3810109A, will continue to be followed for safety purposes according to the study schedule of activities (oral combination ART phase). Participants will not be discontinued or replaced in the study for initiating or changing ART. They will continue to be followed for safety purposes according to the study schedule of evaluations Section 1.3.1. ART regimen changes will be documented in the participant's record. Participants that meet participant level stopping criteria outlined in Section 7.1 will result in a study pause whilst a review of all relevant safety data is performed with the outcomes and recommendations on dosing resumption presented to VSLC for endorsement.

SoC Follow-Up Phase

In the follow-up phase, SoC may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimize the risk of development of resistance.

Guidance is provided below on participant management based on the severity of the AE for specific toxicities in the SOC follow-up phase. All changes in SoC must be accurately recorded in the participant's eCRF.

Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity will continue to be followed for safety purposes according to the study schedule of evaluations (oral combination ART phase). Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by SOC, dosing may continue after discussion with the medical monitor.

Participants who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the SOC should have SOC withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, SOC may be restarted.

Should the same Grade 3 AE recur within 28 days in the same participant, SOC should be permanently discontinued. Changes in SOC will for safety or virologic failure will be made in consultation with the medical monitor and follow international guidelines.

Exceptions are noted for lipid abnormalities in Section 7.1.

Grade 4 Toxicity/Adverse Event

Subjects who develop a Grade 4 AE or toxicity should have SOC discontinued. Changes in SOC will for safety or virologic failure will be made in consultation with the medical monitor and follow international guidelines. However, if the investigator has compelling evidence that the AE is not causally related to the study drugs, dosing may continue after discussion with and assent from the medical monitor. Subjects should be rechecked each week until the AE returns to Grade 2.

Subjects with asymptomatic Grade 4 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to study treatment. Exceptions are noted for lipid abnormalities in Section 7.1.

Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to study treatment are provided below.

Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology during administration of study drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 7 and Section 10.7.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definitions:

Participants of Childbearing Potential (POCBP)

A female at birth 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.

Participants in the following categories are not considered POCBP

1. Premenarchal
    1. 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.

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

10.5.2. Contraception Guidance:

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 7.

Table 7 Highly Effective Contraceptive Methods

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• 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 participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** Failure rate of <1% per year when used consistently and correctly.

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

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

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **ACCEPTABLE METHODS[d]**
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action

• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

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.
d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.
e. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

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

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Section 10.3. 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 or be withdrawn from the study.

10.6. Appendix 6: Genetics

- **USE/ANALYSIS OF DNA**
- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples may be used for research related to GSK3810109A or HIV and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK3810109A or study interventions of this drug class and HIV. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples may be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples may be analyzed for effects on GSK3810109A PK or PD responses, or on HIV susceptibility, severity, or progression. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- Therefore, samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3810109A. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3810109A (or study interventions of this class) or HIV continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Study treatment refers to all drugs evaluated in the study and therefore includes ViiV study intervention and non-ViiV ART therapies that can be used in combination with ViiV products or other ART interventions.

A liver stopping event is an occurrence of predefined liver chemistry changes (ALT, bilirubin) that trigger discontinuation of study treatment and requirement of additional actions and follow up assessments to be performed.

A liver monitoring event is as an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that triggers increased monitoring of the participant's liver chemistries, but no action is taken with study treatment unless liver chemistry stopping criteria are met.

Table 8 Phase 2a Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	**ALT≥3xULN** **If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin), Report as an SAE.** **See additional Actions and Follow Up Assessments listed below**
Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
Immediately discontinue study intervention **Report the event to GSK within 24 hours** **Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]** **Perform liver event follow up assessments** **Monitor the participant until liver chemistries resolve, stabilise, or return**	**Viral hepatitis serology[3]** **Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend** **Obtain blood sample for pharmacokinetic (PK) analysis, obtained CAB of last dose[4]** **Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).** **Fractionate bilirubin, if total bilirubin≥2xULN**

to within baseline (see MONITORING below) **MONITORING:** **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5** **Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours** **Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline** **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 hours** **Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline**	**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.** **Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [James, 2009].** **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 participant 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, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

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. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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10.8. Appendix 8: CDC Classification for HIV-1 Infection (2014)

- Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.
- **HIV infection, stage 0**
  - Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.
- **HIV infection, stage 1**
  - Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.
- **HIV infection, stage 2**
  - Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.
- **HIV infection, stage 3 (AIDS)**
  - Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).
  - Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.
- **HIV infection, stage unknown**
  - Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.
- **Stage-3-defining opportunistic illnesses in HIV infection**
  - Candidiasis of bronchi, trachea, or lungs
  - Candidiasis of oesophagus
  - Cervical cancer, invasive

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

10.9. Appendix 9: Child-Pugh Classification

A participant is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 9). For participants requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 9 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade[1]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

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10.10. Appendix 10: COVID-19 Pandemic and Clinical Trial Continuity

Background

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participants ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to ensure that there are no gaps in HIV-1 treatment for participants enrolled in this clinical study, through continuous access to antiretroviral therapy.

In order to maintain the scientific integrity of the study, and adhere to updated guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate against any impact of COVID-19 are well documented in the trial database.

This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary.

This appendix does not apply to participant management issues that are unrelated to a specific, and documented, impact from COVID-19.

10.10.1. Changes to Study Visits and Study Procedures

If central laboratory testing cannot be performed at a particular visit, and monitoring for safety is required, tests may be performed at an appropriately authorised/accredited local laboratory (or other relevant clinical facility), if this can be done within local restrictions on physical distancing. The site should proactively inform the sponsor about such instances. Local laboratory results may be used to inform safety decisions. Results should be retained in source records.

When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including adverse events, from the participant through alternative means, e.g. by telephone contact.

There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.

There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a

study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

10.10.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as the participant sending a picture of his/her written consent to the investigator, or the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any updated informed consent form or other participant-facing materials should be provided to participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

10.10.3. COVID-19 Vaccines

Any active trial participant who has access via local guidelines to a COVID-19 vaccine that has received emergency, conditional, or standard market authorization may receive that vaccine, if requested by the site investigator and trial participant.

Ideally, when COVID-19 vaccinations are given, administration should occur at least 2 weeks before or after a study visit to allow for a distinctive assessment of any possible ISRs.

As of January 2021, there is limited publicly available information on the reduction of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) transmission after vaccination. Therefore, until further evidence is available and/or local guidance changes, COVID-19 precautions (e.g., masking, social distancing) should be maintained after a vaccination series is completed.

10.10.4. COVID-19 Experimental Agents

If any treatments for COVID-19 are planned for a study participant, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

10.10.5. COVID-19 Specific Data Capture

10.10.5.1. Capturing COVID-19 Specific Protocol Deviations

Please refer to your study procedure manual for specific details on capturing protocol deviations as a result of COVID-19.

10.10.5.2. Capturing COVID-19 Specific AEs and SAEs

It is important for the study team to describe COVID-19 related adverse events/serious adverse and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.

2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.

3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events (related to COVID-19 infection, investigators should use the following Verbatim terms:

    a. Suspected COVID-19 infection; or

    b. Probable COVID-19 infection; or

    c. Confirmed COVID-19 infection

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.

5. A new COVID-19 infection Case Report Form will be added to the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important to collect the correct information from each participant reporting a COVID-19 AE or SAE. Therefore, please use the CRF templates to help you collect this information, once available.

WHO Case Definition - March 20, 2020 Version (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)):

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;

2. Direct physical contact with a probable or confirmed case;

3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR

4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

10.11. Appendix 11: Abbreviations and Trademarks

Abbreviations

ACTG	International AIDS Society
ADA	Anti-drug antibody
CCI [redacted]	
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B Core Antibody
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body Mass Index
bNAb	Broadly neutralizing antibody
BUN	Blood Urea Nitrogen
CA	Competent Authority
CABG	Coronary artery bypass grafting
cART	Combination antiretroviral therapy
c/mL	Copies/milliliter
CDC	Centers for Disease Control and Prevention
CHO	Chinese Hamster Ovary
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
Cmax	Maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CrCl	Creatinine Clearance
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CV	Cardiovascular
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-Drug Interaction
dL	Deciliter
DHHS	Department of Health and Human Services
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DSC	Dose Selection Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECL	Electrochemiluminescence

eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GCSP	GSK's Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GSK3810109A	N6LS
GFR	Glomerular Filtration rate
HAART	Highly active antiretroviral therapy
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormonal replacement therapy
HSR	Hypersensitivity reaction
IAS	International AIDS Society
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed Consent Form
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgM	Immunoglobulin M
INI	Integrase Inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Infusion/ Injection Site Reaction
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IUS	Intrauterine hormone-replacing system
IV	Intravenously
IWRS/IWRS	Interactive Voice/Web Recognition System
LDL	Low density lipoprotein
LOAEL	Lowest observed adverse effect level
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin

MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
µMol/L	Micromole/Liter
mg	Milligram
mg/dL	Milligram per deciliter
mg/min	Milligram per minute
MSD	Meso Scale Discovery
MV	Minimum Value
NAb	Neutralizing Antibody
ng/mL	Nanogram per milliliter
Nm	Nanometer
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OC	Observed Case
CCI [redacted]	
PBS	Phosphate buffered saline
PD	Pharmacodynamic
PEP	Post-exposure prophylaxis
CCI [redacted]	
PK	Pharmacokinetic
POC	Proof of Concept
POCBP	Participants of childbearing potential
PP	Per protocol
PrEP	Pre-exposure prophylaxis
PRO	Protease
PSRAE	Possible suicidality-related adverse event
PT	Prothrombin Time
PTCA	Percutaneous transluminal coronary angioplasty
PTT	Partial Thromboplastin Time
QTc	Corrected QT interval
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT	Reverse Transcriptase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS CoV-2	Severe acute respiratory syndrome coronavirus-2
SC	Subcutaneous
SD	Standard Deviation
SDEC	Safety and Dose Evaluation Committee
SDM	Symptom Distress Module
SoA	Schedule of Activities
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
Tmax	Time to maximal concentration

TV	Target Value
ULN	Upper limit of normal
VLD	Viral load decline
VRC	Vaccine Research Center
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell
WHO	World Health Organization

Trademark Information

Trademarks of ViiV Healthcare
Dovato

Trademarks not owned by the ViiV Healthcare
ACCEPT
GeneSeq
GenoSure
MedDRA
PAXGENE
PhenoSense
SAS
WinNonlin

10.12. Appendix 12: Protocol Amendment History

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

Amendment 1: 01-SEP-2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 1: Liver safety criteria have been updated to align with current ViiV Safety and Labelling Committee guidance. Clarification of allowable visit windows is also provided.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Eligibility criteria have been updated to reflect current ALT and Total Bilirubin eligibility criteria as per ViiV Safety and Labelling Committee (VSLC) Guidance.	Changes made to align to current VSLC Guidance.
7.2 Liver Chemistry Stopping Criteria	Liver stopping criteria have been updated to reflect current ALT and Total Bilirubin eligibility criteria as per VSLC Guidance.	Changes made to align to current VSLC Guidance.
8 Study Assessments and Procedures	Clarification that visit windows are calculated from start of infusion (IV) or time of injection (SC)	Changes made to align with pharmacokinetics analysis plan.

Amendment 2: 05-NOV-2020

CCI

[redacted]

Section # and Name	Description of Change	Brief Rationale
1.3.1 Screening Schedule of Activities	Sample for PBMC collection has been added at the Screening visit.	Sample will be used to support immunology (cell-based) analyses in subjects who enrol in the study. Samples from subjects who do not enrol in the study will be destroyed.
1.3.2 Monotherapy Phase Schedule of Activities	Body weight and height has been added at Day 1 (Pre-dose). CDC Classification has been removed at SOC Initiation and Early Discontinuation visits. Footnote 3 updated regarding timing of initiation of SOC cART.	Changes made for clarification.
1.3.3 Standard of Care Follow-Up Phase Schedule of Activities	HIV Associated conditions have been added at Weeks 4, 8, 16 and 32. PBMC collection has been moved from Week 16 to Week 4.	Changes made for clarification and to adjust immunology sampling timepoints to most relevant timings following SOC initiation.
6.3 Pharmacy Procedures	Storage conditions have been updated to remove temperature excursion allowance.	Changes made to align storage conditions to current product specifications.
8 Study Assessments and Procedures	Visit windows descriptions have been altered.	Changes made for clarity in calculating visit windows. (Actual visit windows have not changed)
8.7.2 T-cell Responses	T cell investigation description has been updated.	Changes made for clarity.

Amendment 3: 11-MAR-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 3: Additional exclusion criteria and study participant monitoring during Day 1 has been included in this amendment. Clarifications regarding parallel enrollment during Parts 1 and 2, study pause criteria, use of COVID-19 vaccines during the study, and choice of standard of care ART have been included.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Study cohorts within Part 1 and Part 2 will be enrolled as parallel, randomized groups. A "No Go" decision by SDEC will apply to all subsequent dosing groups	Changes made for clarification.
1.3.2 Monotherapy Phase Schedule of Activities	Study participants will be required to remain in clinic from Pre-dose through 4 hours for monitoring of vital signs. Vital signs of blood pressure, heart rate, body temperature and SPO2 will be recorded in the eCRF during and for up to 4 hours following the infusion/injection. Vital signs including blood pressure, heart rate, body temperature, respiratory rate and SpO2 must be obtained every 15 minutes during the infusion period (only required Pre-Dose and Post-Dose for SC injections), every 30 minutes for two hours following the start of the infusion/ injection, and then hourly for another two hours; vital signs should be recorded in the medical record.	Additional monitoring requirements have been added during Day 1.
4.1.3 Standard of Care Follow-Up Phase	A regimen of dolutegravir + lamivudine will be provided through the study if deemed appropriate by the investigator and consistent with local guidelines.	Clarification that choice of SOC regimen should be consistent with applicable guidelines.
4.2 Scientific Rationale for Study Design	Oral dolutegravir + lamivudine (Dovato™) will be provided in the study for use during the SOC follow-up period, if appropriate and consistent with local Guidelines.	Clarification that choice of SOC regimen should be consistent with applicable guidelines.

Section # and Name	Description of Change	Brief Rationale
4.4 Interim Go / No Go Criteria and Dose Selection	If a No Go decision is reached, this will apply to all subsequent planned cohorts.	Clarification that No Go decision will apply to all subsequent cohorts.
5.2 Exclusion Criteria	Hemoglobin ≥ Grade 2 (Males: <10 g/dl; Females <9.5 g/dL). A single repeat test is allowed during the Screening period to verify a result. Platelets ≥Grade 2 (<100,000 cells/mm^3). A single repeat test is allowed during the Screening period to verify a result. PT ≥Grade 2 (≥1.25 ULN). A single repeat test is allowed during the Screening period to verify a result. INR ≥Grade 2 (≥1.5 ULN). A single repeat test is allowed during the Screening period to verify a result. Absolute Neutrophil Count (ANC) ≥Grade 2 (ANC ≤799 cells/mm^3). A single repeat test is allowed during the Screening period to verify a result.	Changes made to exclude subjects at elevated risk of infection or bleeding disorder.
6.1 Study Intervention(s) administered	Study arm updated, and dose formulation changed to “Solution for injection or infusion”	Clarification of the descriptors within Table 2.

Section # and Name	Description of Change	Brief Rationale
10.10.3 COVID-19 Vaccines	COVID-19 vaccines approved under emergency, conditional or standard authorization are allowed, in addition to guidance on timing and transmission reduction strategies.	Clarification on the use of COVID-19 vaccines during the study.

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