TITLE PAGE

Protocol Title: A Phase 1, Open-Label, Single-Dose Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, GSK3810109, Administered Either Subcutaneously with Recombinant Human Hyaluronidase PH20 (rHuPH20) or Intravenously, to Healthy Adults

Protocol Number: 217901/Amendment 02

Compound Number or Name: GSK3810109

Study Phase: Phase 1

Brief Title: A study to investigate the safety and pharmacokinetics of a single dose of GSK3810109 administered either subcutaneously with rHuPH20 or intravenously, in healthy adult participants

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Regulatory Agency Identifying Number(s):US IND: 148241

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

Sponsor Signatory
Scott McCallister, Head Physician
ViiV Healthcare and Development

Approval Date: 26 Sep 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 02	26 Sep 2022	TMF- 14965235
Amendment 01	03 June 2022	TMF-14645038
Original Protocol	25 January 2022	TMF-14419933

Amendment 02: 26 Sep 2022

Overall Rationale for the Amendment: The protocol is amended to include an additional dosing group CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Throughout the document, as applicable	• Sections were modified to accommodate additional subcutaneous dosing group, designated as Part 3 of the study • CCI [redacted]	CCI [redacted]
Section 1.6 Schedule of Activities (SoA) Part 2	• Modified SoA for Part 2 to correct headers, include electrocardiogram (ECG) at end of infusion, and to add missing elements • Increased frequency of clinical laboratory monitoring (Day 2 through Day 8 while in the clinic) in SoA for Part 2	• SoA of Part 2 of the study has been identified to have incorrect headers, formatting errors, and missing elements from the list of clinical activities. • As per FDA feedback to increase frequency of clinical laboratory monitoring because there are no clinical data with doses of GSK3810109 greater than 40 mg/kg as a single administration.
Section 1.1 Synopsis	Safety Review Team composition	To reflect correct composition as

Section # and Name	Description of Change	Brief Rationale
	was modified	mentioned in Section 10.1.5
Section 1.5 Schedule of Activities (SoA) Part 1	Part 1 SoA corrected to remove footnote number for predose ECG and footnote number for HIV and hepatitis B and C was updated	Errors inadvertently introduced in Amendment 1 were corrected.
Section 1.6 Schedule of Activities (SoA) (Part 2)	Notes section	This section was added to provide clarity on activities for Part 2 study assessments
Section 4.1 Overall Design	Dose definition at dose of 2000 U/mL or ~28,000 U for a 70 kg participant was added	Added clarification on the dosing
Section 5.2 Exclusion criteria	Exclusion criterion of positive hepatitis C antibody test was added	This exclusion criterion was not previously included, although the hepatitis C antibody test was performed by the clinic and a negative result was required prior to study entry.
Throughout the document	Minor formatting, administrative, and language changes were made	For clarity and better readability

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Single-Dose Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, GSK3810109, Administered Either Subcutaneously with Recombinant Human Hyaluronidase PH20 (rHuPH20) or Intravenously, to Healthy Adults

Brief Title: A study to investigate the safety and pharmacokinetics of a single dose of GSK3810109 administered either subcutaneously with rHuPH20 or intravenously, in healthy adult participants.

Rationale: GSK3810109 is a human monoclonal antibody active against human immunodeficiency virus (HIV) that can mediate extraordinary breadth and potency against various HIV isolates, including strains traditionally resistant to other antibodies in this class.

This study is designed to evaluate safety, tolerability, and pharmacokinetic (PK) endpoints in healthy adult participants when GSK3810109 is administered as either subcutaneous (SC) injection (Part 1 and Part 3 of study) or by intravenous (IV) infusion (Part 2 of study). Dosing by either SC or IV infusion may each offer practical advantages related to tolerability, simplicity, or frequency of dosing in the administration of GSK3810109.

Administration by SC Infusion

While broadly neutralizing antibodies have typically been administered at doses requiring IV infusions, the potency of GSK3810109 may enable lower doses of the antibody to mediate an effect. The ability to administer GSK3810109 as a SC injection may offer several advantages over IV infusion, including fewer complications, less pain, and ease of administration, especially with chronic dosing.

The rHuPH20 enzyme facilitates SC delivery of co-administered therapeutics. Hyaluronidase injection is effective for use as an adjunct to increase the absorption and dispersion of other injected drugs, including for hypodermoclysis and as an adjunct in SC urography for improving the resorption of radiopaque agents. The use of rHuPH20 with GSK3810109 offers the potential to administer a larger volume of the antibody than could be administered alone (~2.0 mL). The current study will investigate the ability to deliver a larger SC dose of GSK3810109 (20 mg/kg, up to 24 mL [Part 1] or CCI [redacted] in combination with rHuPH20. The rHuPH20 will be co-mixed with GSK3810109 at a concentration of 2000 U/mL based on the dosing volume of GSK3810109 (variable dose/volume of rHuPH20 for the 20 mg/kg dose level; CCI [redacted] Thus, for Part 1, the maximum volume needed to administer a SC dose is not expected to exceed 24 mL. For Part 3, CCI [redacted]

Administration by IV Infusion

There is a practical limitation for administration of high doses of GSK3810109 via SC infusion. To date, the maximum dose administered via SC route is 20 mg/kg in combination with rHuPH20, while an IV route allows higher dose administration. In this study, an IV dose of 60 mg/kg of GSK3810109 will be administered, which offers the potential for an ultra-long-acting target profile to support administration every 4 to 6 months, thus reducing dosing frequency and potentially improving adherence and acceptability. Medication adherence and decreasing frequency of clinic visits is the most important determinant for sustained viral suppression and long-term treatment success.

GSK3810109 dose has not exceeded 40 mg/kg in humans as a single administration. Pharmacokinetic modeling suggests a 60 mg/kg dose may be adequate for every 4 to 6 months administration. The no-observed-adverse-effect level (NOAEL) set by the Vaccine Research Center (VRC) is at 400 mg/kg IV and was endorsed by the FDA. Based on the same VRC generated data, ViiV Healthcare set the NOAEL at 40 mg/kg based on the morbidity of one male rat at 400 mg/kg, for which it was not possible to exclude a relationship to exposure.

A review of observed GSK3810109 Cmax and area under the plasma concentration-time curve (AUC) exposure in humans at 40 mg/kg IV found levels to be appreciably higher than rodent exposures at the GSK/ViiV 40 mg/kg NOAEL. This suggests the rodent NOAEL set at 40 mg/kg may be less relevant in humans as a maximum ceiling dose. In addition, simulated PopPK modeling show that 60 mg/kg IV in humans are predicted to have a lower Cmax than the VRC 400 mg/kg rat NOAEL Cmax.

The inclusion of both routes of administration in this study is an efficient design to enable rapid progression to future studies using either 1 or both routes of administration.

Objectives and Endpoints and Estimands:

Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of a single dose of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants	**Part 1 and Part 3 (SC injection)** • The number and percentages of participants who have AEs (Grade 2 or higher) and SAEs following GSK3810109 SC administration through Week 24 • The number and percentages of participants who have ISRs within 7 days following GSK3810109 SC administration • The incidence of Grade 2 to 4 elevated ALT/AST following GSK3810109 SC

Objectives	Endpoints
	administration **Part 2 (IV infusion)** • The number and percentages of participants who have AEs and SAEs following GSK3810109 IV administration through Week 24 • The incidence of Grade 2 to 4 elevated ALT/AST following GSK3810109 IV administration through Week 24
Secondary	
• To evaluate the PK of a single dose of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants	• Assessment of GSK3810109 PK parameters including AUC(0-inf), AUC(0-t), Cmax, Tmax, and t1/2 (if possible)
• To assess the severity and acceptance of pain and ISRs after SC administration of GSK3810109 with rHuPH20	• Dimension score "acceptance of ISRs" and individual item score assessing pain at Day 2 and Day 7 using the PIN Questionnaire • Proportion of participants who are bothered or affected by the pain and local reactions as a result of the injection as measured by the PIN on Days 2 and 7 • Post-injection pain assessment using NRS at Days, 1, 2, and 7 • The incidence and duration of ISRs assessed overall and by grade including the duration at grade
• To assess the severity of pain after IV administration of GSK3810109	• Post-infusion pain assessment using NRS at Days, 1, 2, and 7
• To evaluate additional safety parameters following administration of GSK3810109 SC with rHuPH20 or IV in healthy adult participants	• Change from baseline in clinical laboratory assessments, ECGs, and vital sign measurements
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

CCI [redacted]; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC(0-inf) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the plasma concentration-time curve from time zero to time of last observed quantifiable concentration; Cmax = maximum observed concentration; ECG = electrocardiogram; ISR = injection site reaction; IV = intravenous (ly) NRS = Numeric Rating Scale; PIN = Perception of Injection; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous (ly); t1/2 = apparent terminal phase half-life; Tmax = time of maximum observed concentration.

Overall Design:

This is an open-label, single-dose study to assess the safety, tolerability, and PK of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants

This study will comprise 3 parts:

In Part 1, approximately 8 participants will receive a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20 at a dose of 2000 U/mL or ~28,000 U for a 70 kg participant. The participants will be admitted in the clinic on Day –1 and the study product will be administered on Day 1. The participants will remain in the clinic for approximately 8 hours for study-related procedures after study product administration and will be followed up for 24 weeks.

Safety laboratory samples will be collected throughout the study as per the Schedule of Activities (SoA). The primary endpoint of injection site reaction (ISR) will be evaluated at specified time points up to Day 7; study participants will keep a diary of ISRs for 14 days after study product administration. Symptoms, maximum intensities, and durations will be reported through end of study to characterize presentation and resolution of local ISRs.

In Part 2, approximately 8 participants will receive a single 60 mg/kg IV dose of GSK3810109. A sentinel cohort of 2 participants will be used to mitigate the risk of unexpected AEs prior to dosing of the remaining 6 participants, who will be dosed in sequential cohorts of 2 participants each.

The sentinel cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks.

Following Day 10 visit, core Safety Review Team (SRT) will review the safety data (safety laboratory data, electrocardiogram, and AEs) from the sentinel cohort and may

recommend continuation of the study where the next cohort of 2 participants will be dosed.

The second cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks. A review of at least AE data from this cohort will be conducted after a minimum of 4 days following infusion of GSK3810109 and the core SRT may recommend continuation of the study where the next cohort of 2 participants will be dosed.

The third cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks. A review of at least AE data from this cohort will be conducted after a minimum of 4 days following infusion of GSK3810109 and the core SRT may recommend continuation of the study into the fourth cohort of 2 participants.

The fourth cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks.

Safety laboratory samples will be collected throughout the study as per the SoA.

CCI [redacted] An initial cohort of 2 participants will be used to mitigate the risk of unexpected AEs prior to dosing of the remaining 6 participants.

In the first cohort, 2 participants will be admitted in the clinic on Day –1 and the study product will be administered on Day 1. The participants will remain in the clinic and be monitored for 3 days after study product administration. The participants will be discharged from the clinic on Day 4 and will be followed up for 24 weeks. Following discharge, core SRT will review at least AE data and may recommend continuation of the study where the next cohort of 6 participants will be dosed.

The second cohort of 6 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 3 days after study product administration. The participants will be discharged from the clinic on Day 4 and will be followed up for 24 weeks.

Safety laboratory samples will be collected throughout the study as per the SoA. The primary endpoint of ISR will be evaluated at specified time points up to Day 7; study participants will keep a diary of ISRs for 14 days after study product administration.

Symptoms, maximum intensities, and durations will be reported through end of study to characterize presentation and resolution of local ISRs.

Note: Results of Part 3 will be reported separately from Part 1 and Part 2.

Interim Analysis

An interim analysis is planned after all participants receiving SC administration in Part 1 complete their Week 24 visit. At that time point, the data available for participants receiving IV administration will also be analyzed and included.

Brief Summary:

The purpose of this study is to assess the safety, tolerability, and PK of a single 20 mg/kg or CCI [redacted] or a single 60 mg/kg IV dose of GSK3810109, in healthy adult participants.

- Study duration: Up to 24 weeks excluding screening
- Treatment duration:
  - For Part 1, single SC infusion on Day 1 that is expected to take 3 to 15 minutes to administer.
  - For Part 2, single IV infusion on Day 1, that is expected to take approximately 60 minutes to administer; the entire infusion should not exceed 2 hours.
  - CCI [redacted]

Number of Participants:

A sufficient number of participants will be enrolled to ensure that approximately 8 participants complete each part of the study for a total of approximately 24 participants in the study.

Participants who withdraw prior to study completion may be replaced.

Note: Enrolled means a participant's agreement to participate in a clinical study following completion of the informed consent process and all screening activities. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Intervention Groups and Duration:

The study duration will be 24 weeks (excluding screening) and the study product will be administered on Day 1 of each part.

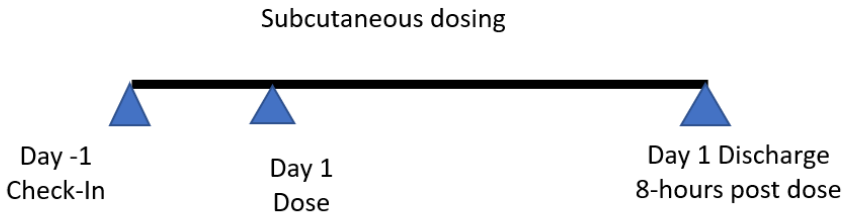
Data Monitoring/ Other Committee: No Data and Safety Monitoring Board will be empaneled for this study

An SRT for GSK3810109 reviews emerging and cumulative data for GSK3810109 on a monthly basis. For Part 1, safety review decisions and the status of the enrollment process will be shared with an SRT at regular intervals and discussed during the monthly SRT meetings.

For Part 2, a core SRT for Study 217901 will review data for both sentinel and non-sentinel participants of the study. CCI [redacted] The core SRT is composed of safety lead, medical monitors, and project biostatistician.

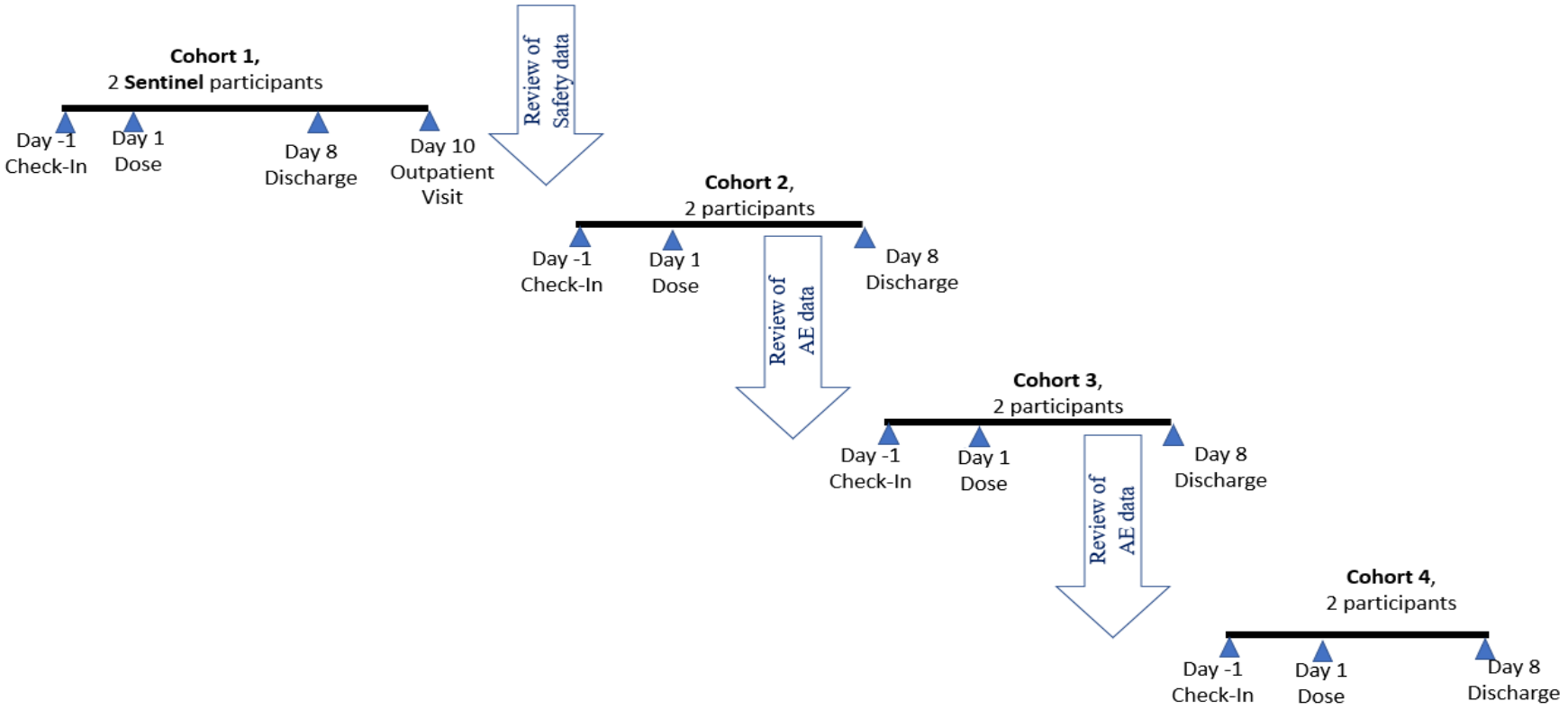
The SRT will make recommendations to the ViiV Safety and Labelling Committee (VSLC) regarding safety findings, including study pause, modification, and termination. The VSLC is chaired by the ViiV Chief Medical Officer and will have the final decision on study modifications, including termination. Details regarding the VSLC membership and function are included within the VSLC Charter.

1.2. Schema (Part 1)



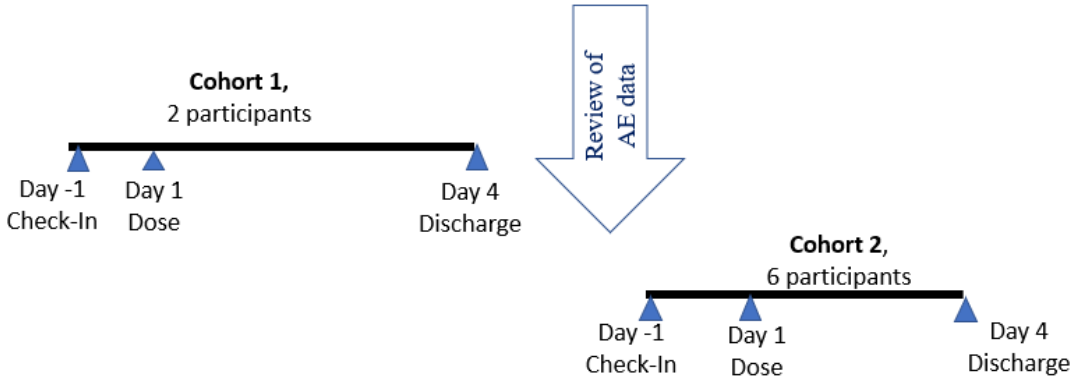
N= 8; All participants will receive a single 20 mg/Kg SC dose of GSK3810109 co-administered with rHuPH20 and be followed up for 24-weeks

1.3. Schema (Part 2)



N= 8; All participants will receive a single 60 mg/Kg IV dose of GSK3810109, and be followed up for 24-weeks

1.4. Schema (Part 3)



CCI [redacted]

1.5. Schedule of Activities (SoA) Part 1

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**ED = early discontinuation/withdrawal**
Time From Start of SC Infusion			**Pre**	**SOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**				**Follow-up**												
Informed consent	X																		
Admission to clinic		X																	
Discharge from clinic						X													
Inclusion and exclusion criteria	X	X																	
Demographics	X																		
Height, weight, and BMI[2]	X	X	X																
Vital signs[3]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4]	X	X	X			X													X
Drug Alcohol/Cotinine /history and screen[5]	X	X																	

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**ED = early discontinuation/withdrawal**
Time From Start of SC Infusion			**Pre**	**SOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**				**Follow-up**												
Past and Current medical conditions	X	X																	
Study product administration				X															
PIN and NRS[6]				X			X			X									
12-lead ECG[7]	X		X		X		X	X	X	X			X					X	
Clinical laboratory[5]	X	X					X			X	X		X			X		X	X
Urinalysis[5]	X	X									X								
Pregnancy test:(serum) (POCBP only)[8]	X	X					X			X	X		X	X	X	X	X	X	X
FSH[9]	X																		
HIV and hepatitis B and C[5]	X																		
Test for SARS-CoV-2[10]	X	X																	

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**ED = early discontinuation/withdrawal**
Time From Start of SC Infusion			**Pre**	**SOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**				**Follow-up**												
Timed PK sample[11]			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted] sample collection			X										X	X	X	X	X	X	X
Recording of injection site reactions in 14 days diary card[12]				←	—	—	—	—	—	—	→								
Recording of AEs/SAEs[13]				←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X
Concomitant medication review			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BMI = body mass index; COVID-19 = coronavirus disease; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus-1; ISR = injection site reaction; NRS = Numeric Rating Scale; PIN = Perception of Injection PK = pharmacokinetic(s); POCBP = participant of childbearing potential; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus-2; SC = subcutaneous; SOI = start of infusion

Visit windows: Schedule Visits 01 through 13 with respect to Day 1. Visit 01 (-10 minutes for PK sample collection and vitals; -1 hour for ECG), Visit 01A (+10 minutes); Visits 01B and 01C (±10 minutes); Visits 02, 03, and 04 (±6 hours); Visits 05, 06, 07, and 08 (±2 days), and Visits 09, 10, 11, 12, and 13 (±7 days).

1 Day 1 = day of product administration. The screening period will preferably be 14 days but may be extended to 21 days to allow for the possibility of study pauses or scheduling difficulty with the approval of the investigator. Day 1 evaluations prior to product administration will be considered as baseline for assessing subsequent AEs. [Note: Participants will remain in the clinic for approximately 8 hours for study-related procedures after study product administration].

2 Height and weight will be measured and BMI will be calculated at Screening. Only weight will be measured at Check-in and Day 1.

3 Vital signs will include body temperature, systolic and diastolic blood pressure, respiratory rate, and pulse. The Oxygen saturation (SPO_2) will also be measured during the in-clinic period on Day 1. For further details, refer to Section 8.1.2.

4 A full physical examination will be performed at Screening (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination (at minimum, assessment of skin, lungs, cardiovascular system, and abdomen [liver and spleen]) will be performed at Check-in, at Day 1 (predose), at 8 hours, and at ED visit. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

5 A complete list of assessments is provided in Section 10.2.

6 NRS will be administered on Day 1 at the end of the infusion. Additionally, PIN and NRS will be administered on Day 2 and Day 7.

7 The electrocardiogram (ECG) taken at Screening and on Day 1 before product administration will be a single reading; however, repeat ECGs are allowed at investigator's discretion to confirm the eligibility. Triplicate 12-lead ECGs will be obtained for all postdose time points.

8 At the Day –1 visit, a serum sample will be sent for pregnancy testing. Pregnancy testing will be conducted on POCBP only on serum samples. Refer to Section 8.1.5.

9 Females with at least 12 months of amenorrhea must have a serum FSH test performed at Screening to confirm postmenopausal status.

10 The clinic will follow their standard procedures and/or local guidelines with respect to COVID-19 testing at Screening, enrollment, and any other time points during the study, if deemed necessary by the investigator.

11 The PK blood draw "visits" are defined relative to the exact time of the end of infusion. The exact start and end times of product administration and the time of PK blood draw(s) will be recorded to ensure accurate PK analysis. All participants will be observed for 4 hours after product administration.

12 An ISR that is considered Grade 3 or greater may be referred for dermatology consult and workup (dermatology referral for Grade 3 erythema without other local symptoms will be at the discretion of the investigator). Please refer to Section 8.2.7.1 for further details.

13 Please refer to Section 8.2.1 for study participation related SAEs.

Notes

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing 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 the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.
- The Competent Authority (CA) 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 CA and the EC before implementation.

1.6. Schedule of Activities (SoA) (Part 2)

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**ED = early discontinuation/withdrawal**
Time From Start of IV Infusion			**Pre**	**EOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk2**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D8**	**D10[2]**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**									**Follow-up**									
Informed consent	X																				
Admission to clinic		X																			
Discharge from clinic											X										
Inclusion and exclusion criteria	X	X																			
Demographics	X																				
Height, weight, and BMI[3]	X	X	X																		
Vital signs[4]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[5]	X	X	X	X		X						X									X
Drug Alcohol/Cotinine /history and screen[6]	X	X																			

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**ED = early discontinuation/withdrawal**
Time From Start of IV Infusion			**Pre**	**EOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk2**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D8**	**D10[2]**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**									**Follow-up**									
Past and Current medical conditions	X	X																			
Study product administration[7]				X																	
NRS				X			X			X											
12-lead ECG[8]	X		X	X	X		X	X	X	X	X	X			X					X	
Clinical laboratory[6]	X	X					←	—	—	—	→	X	X		X			X		X	X
Urinalysis[6]	X	X										X	X								
Pregnancy test:(serum) (POCBP only)[9]	X	X					X			X			X		X	X	X	X	X	X	X
FSH[10]	X																				
HIV and hepatitis B and C[6]	X																				

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**ED = early discontinuation/withdrawal**
Time From Start of IV Infusion			**Pre**	**EOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk2**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D8**	**D10[2]**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**									**Follow-up**									
Test for SARS-CoV-2[11]	X	X																			
Timed PK sample[12]			X	X	X		X	X	X	X			X	X	X	X	X	X	X	X	X
CCI																					
Recording of AEs/SAEs[13]				←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X
Concomitant medication review			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X

AE = adverse event; BMI = body mass index; COVID-19 = coronavirus disease; EOI = end of infusion; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; IV-intravenous; NRS = Numeric Rating Scale; PK = pharmacokinetic(s); POCBP = participant of childbearing potential; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus-2

Visit windows: Schedule Visits 01 through 15 with respect to Day 1. Visit 01 (-10 minutes for PK sample collection and vitals; -1 hour for ECG), Visit 01A (window for start of infusion +10 minutes); Visits 01B and 01C (±10 minutes); Visits 02, 03, 04, 05, 06 (±6 hours), Visit 07 (±12 hours); Visits 08, 09, 10 (±2 days), and Visits 11, 12, 13, 14, and 15 (±7 days). Assessments should be done as close as possible to nominal time.

1 Day 1 = day of product administration. Day 1 evaluations prior to product administration will be considered as baseline for assessing subsequent AEs.

2 Day 10 outpatient visit is only applicable to 2 sentinel participants.

3 Height and weight will be measured and BMI will be calculated at Screening. Only weight will be measured at Check-in and Day 1

4 Vital signs will include body temperature, systolic and diastolic blood pressure, respiratory rate, and pulse. On Day 1, the vital signs and SPO_2 will be measured at predose, every 15 minutes from start of infusion for 2 hours, and at 4 hours and 8 hours postdose. For further details, refer to Section 8.1.2

5 A full physical examination will be performed at Screening (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination (at minimum, assessment of skin, lungs, cardiovascular system, and abdomen [liver and spleen]) will be performed at Check-in, at Day 1 (pre-dose), at 8 hours, Day 10 (applicable only for 2 sentinel participants) and at ED visit. A brief physical examination will also be performed within 30 to 60 minutes of EOI. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

6 A complete list of assessments is provided in Section 10.2.

7 Study product administration will be performed following predose activities.

8 The electrocardiogram (ECG) taken at Screening and on Day 1 before product administration will be a single reading; however, repeat ECGs are allowed at investigator's discretion to confirm the eligibility. Triplicate 12-lead ECGs will be obtained for all postdose time points. For Visit 01A, ECGs will be taken within 30 minutes of EOI.

9 At the Day –1 visit, a serum sample will be sent for pregnancy testing. Pregnancy testing will be conducted on POCBP only on serum samples. Refer to Section 8.1.5.

10 Females with at least 12 months of amenorrhea must have a serum FSH test performed at screening to confirm postmenopausal status.

11 The clinic will follow their standard procedures and/or local guidelines with respect to COVID-19 testing at Check-in, during the intervention period, and at any other time points during the study, if deemed necessary by the investigator. The Covid test during the screening period should be performed within -7 days of check in.

12 The PK blood draw "visits" are defined relative to the exact time of the end of infusion. The exact start and end times of product administration and the time of PK blood draw(s) will be recorded to ensure accurate PK analysis.

13 All AEs/SAEs will be collected from the start of study product infusion. Please refer to Section 8.2.1 for study participation related SAEs.

Notes

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing 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 the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.
- The Competent Authority (CA) 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 CA and the EC before implementation.

1.7. Schedule of Activities (SoA) Part 3

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**ED = early discontinuation/withdrawal**
Time From Start of SC Infusion			**Pre**	**EOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**							**Follow-up**									
Informed consent	X																		
Admission to clinic		X																	
Discharge from clinic									X										
Inclusion and exclusion criteria	X	X																	
Demographics	X																		
Height, weight, and BMI[2]	X	X	X																
Vital signs[3]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4]	X	X	X			X													X
Drug Alcohol/Cotinine /history and screen[5]	X	X																	

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**ED = early discontinuation/withdrawal**
Time From Start of SC Infusion			**Pre**	**EOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**							**Follow-up**									
Past and Current medical conditions	X	X																	
Study product administration[6]				X															
PIN and NRS[7]				X			X			X									
12-lead ECG[8]	X		X		X		X	X	X	X			X					X	
Clinical laboratory[5]	X	X					X	X	X	X	X		X			X		X	X
Urinalysis[5]	X	X									X								
Pregnancy test:(serum) (POCBP only)[9]	X	X					X			X	X		X	X	X	X	X	X	X
FSH[10]	X																		
HIV and hepatitis B and C[5]	X																		
Test for SARS-CoV-2[11]	X	X																	

Visit Number			**01**	**01A**	**01B**	**01C**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**ED = early discontinuation/withdrawal**
Time From Start of SC Infusion			**Pre**	**EOI**	**4hr**	**8hr**	**24hr**	**48hr**	**72hr**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	
Day of Study[1]		**D-1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D4**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	
Clinical Activity	**Screen Days -21 to -2**	**Check-in**	**Intervention Period**							**Follow-up**									
Timed PK sample[12]			X	X[13]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																			
Recording of injection site reactions in 14 days diary card[14]				←	—	—	—	—	→										
Recording of AEs/SAEs[15]				←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X
Concomitant medication review			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X

AE = adverse event; BMI = body mass index; COVID-19 = coronavirus disease; EOI = end of infusion; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus-1; ISR = injection site reaction; NRS = Numeric Rating Scale; PIN = Perception of Injection PK = pharmacokinetic(s); POCBP = participant of childbearing potential; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus-2; SC = subcutaneous; SOI = start of infusion

Visit windows: Schedule Visits 01 through 13 with respect to Day 1. Visit 01 (-10 minutes for PK sample collection and vitals; -1 hour for ECG), Visit 01A (+10 minutes); Visits 01B and 01C (±10 minutes); Visits 02, 03, and 04 (±6 hours); Visits 05, 06, 07, and 08 (±2 days), and Visits 09, 10, 11, 12, and 13 (±7 days). Assessments should be done as close as possible to nominal time.

1 Day 1 = day of product administration. Day 1 evaluations prior to product administration will be considered as baseline for assessing subsequent AEs.

2 Height and weight will be measured and BMI will be calculated at Screening. Only weight will be measured at Check-in and Day 1.

3 Vital signs will include body temperature, systolic and diastolic blood pressure, respiratory rate, and pulse. on Day 1, the vital signs and SPO_2 will be measured at pre-dose and at 4 hours and 8 hours postdose. For further details, refer to Section 8.1.2.

4 A full physical examination will be performed at Screening (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination (at minimum, assessment of skin, lungs, cardiovascular system, and abdomen [liver and spleen]) will be performed at Check-in, at Day 1 (predose), at 8 hours, and at ED visit. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

5 A complete list of assessments is provided in Section 10.2.

6 Study product administration will be performed following predose activities

7 NRS will be administered on Day 1 at the end of the infusion. Additionally, PIN and NRS will be administered on Day 2 and Day 7.

8 The electrocardiogram (ECG) taken at Screening and on Day 1 before product administration will be a single reading; however, repeat ECGs are allowed at investigator's discretion to confirm the eligibility. Triplicate 12-lead ECGs will be obtained for all postdose time points.

9 At the Day –1 visit, a serum sample will be sent for pregnancy testing. Pregnancy testing will be conducted on POCBP only on serum samples. Refer to Section 8.1.5.

10 Females with at least 12 months of amenorrhea must have a serum FSH test performed at screening to confirm postmenopausal status.

11 The clinic will follow their standard procedures and/or local guidelines with respect to COVID-19 testing at Check-in and during the intervention period, and any other time points during the study, if deemed necessary by the investigator. The Covid test during the screening period should be performed within -7 days of check-in.

12 The PK blood draw "visits" are defined relative to the exact time of the end of infusion. The exact start and end times of product administration and the time of PK blood draw(s) will be recorded to ensure accurate PK analysis. All participants will be observed for 4 hours after product administration. Plasma samples of approximately 2 mL will also be collected for rHuPH20 analysis at predose, 1 and 4 hours after the end of infusion.

13 PK blood samples will be collected at end of infusion for GSK3810109 PK analysis and at 1 hour after end of infusion for rHuPH20 analysis.

14 An ISR that is considered Grade 3 or greater may be referred for dermatology consult and workup (dermatology referral for Grade 3 erythema without other local symptoms will be at the discretion of the investigator). Please refer to Section 8.2.7.1 for further details.

15 All AEs/SAEs will be collected from the start of study product infusion. Please refer to Section 8.2.1 for study participation related SAEs.

Notes

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing 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 the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

The Competent Authority (CA) 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 CA and the EC before implementation

2. INTRODUCTION

Despite significant progress in the treatment and prevention of human immunodeficiency virus (HIV) infection, HIV/(acquired immunodeficiency syndrome) AIDS has remained a major global public health problem since the discovery of the virus in 1983. Reports by the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimate that 79.3 million people have been infected with HIV since the start of the epidemic, contributing to 36.3 million deaths from AIDS-related illnesses [UNAIDS, 2021]. Despite these statistics, global incidences of new HIV infections have actually declined from peak rates in the mid-1990s; a reduction attributed in part to increased availability of antiretroviral therapy (ART) and the effective execution of prevention/treatment programs such as those that target mother-to-child transmission. Unfortunately, HIV infection is extremely complex and none of the current therapeutic regimens can cure an infection or induce a full recovery of the host immune system. Long-term toxicities, emergent and transmitted drug resistance, and drug-drug interactions create a continued unmet medical need for new antiretroviral medications (with new modes of action). Current approved treatment therapies require daily therapy. Thus, novel therapeutic strategies are being investigated.

The Vaccine Research Centre (VRC)/National Institute of Allergy and Infectious Diseases is investigating clinical applications of broadly neutralizing human monoclonal antibodies (bNAbs) that bind the HIV type 1 (HIV-1) envelope protein [Huang, 2016; Huang, 2012;

Kwon, 2012; Wu, 2010]. Such antibodies block infection of target cells in vitro and have been shown to prevent infection of non-human primates in in vivo models for HIV [Mascola, 2000; Pegu, 2014; Rudicell, 2014]. Through advances in B-cell immunology utilizing single-cell cloning methods, next-generation sequencing, high throughput computational analysis techniques, and increased cell culture survivability procedures, an extensive group of HIV-1 bNAbs have been isolated. These include an HIV-1 specific bNAb identified as N6 that was recently isolated from a patient with a 21-year known history of HIV-1 infection that was controlled in the absence of ART [Huang, 2016].

In order to improve the pharmacokinetics (PK) of N6, 2 amino acid substitutions (methionine to leucine and an asparagine to serine M428L/N434S, that collectively yielded N6LS [GSK3810109]) were introduced within the C-terminus of the heavy chain constant region of N6 via site-directed mutagenesis to increase its binding affinity for the neonatal Fc-receptor (FcRn). This modification results in enhanced recirculation and longer plasma half-life of GSK3810109 relative to the wild-type Ab.

GSK3810109 is being developed for the prevention of HIV-1 infection in uninfected adults and for treatment of HIV-1 infection in infected adults. The first-time-in-human (FTIH) study (VRC 609) is currently ongoing to evaluate the safety, tolerability, and PK of this antibody.

2.1. Study Rationale

GSK3810109 (identified as N6LS and VRC-HIVMAB091-00-AB in scientific reports), is a highly potent and broadly neutralizing monoclonal antibody directed against the CD4-binding site of the HIV-1 envelope glycoprotein 120 subunit (gp120). GSK3810109 can mediate extraordinary breadth and potency against various HIV isolates, including strains traditionally resistant to other antibodies in this class.

This study is designed to evaluate safety, tolerability, and PK endpoints in healthy adult participants, when GSK3810109 is administered as either subcutaneous (SC) injection (Part 1 and Part 3 of study) or by intravenous (IV) infusion (Part 2 of study). Dosing by either SC or IV infusion may each offer practical advantages related to tolerability, simplicity, or frequency of dosing in the administration of GSK3810109. The inclusion of both routes of administration in this study is an efficient design to enable rapid progression to future studies using either 1 or both routes of administration.

This current study is aimed at investigating options that may reduce the frequency of administration and thus the burden on patients by evaluating the feasibility of a high dose of GSK3810109 administered IV, and larger SC dose volumes (>2.5 mL) of GSK3810109 using a 20 mg/kg or CCI

In this study, an IV dose of 60 mg/kg of GSK3810109 will be administered, which may offer the potential for an ultra-long-acting target profile to support administration every 4 to 6 months, thus improving adherence. Medication adherence and decreasing frequency of clinic visits is the most important determinant for sustained viral suppression and long-term treatment success.

The rHuPH20 enzyme facilitates the SC delivery of co-administered therapeutics. Hyaluronidase injection is effective for the use as an adjunct to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; as an adjunct in SC urography for improving the resorption of radiopaque agents (United States Federal Register [23 September 1970]).

The FTIH Protocol VRC 609 study is currently ongoing to evaluate the safety, tolerability, and PK of GSK3810109 (N6LS). As of 4 August 2021, no significant safety findings were noted. Two Grade 3 events of injection site erythema, one after receiving 5 mg/kg SC N6LS + 2000 U rHuPH20/mL and one after receiving 20 mg/kg SC N6LS + 2000 U rHuPH20/mL, were noted; however, the Grade 3 erythema observed in both individuals was well tolerated and judged to not represent an increased safety risk for study participants.

2.2. Background

2.2.1. GSK3810109

GSK3810109 belongs to a class of broadly neutralizing HIV antibodies. These antibodies target the CD4-binding site of the HIV envelope protein.

Protocol VRC 609, the FTIH study of GSK3810109 (N6LS) in healthy individuals assesses the safety, tolerability, and PK of this antibody. The FTIH study is an open-label, single- and repeat-dose administration of GSK3810109 (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=4), 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). Thus, in total, 23 participants were enrolled and 22 participants completed the study as of 04 Aug 2021. One participant was terminated from the study after enrolling but prior to product administration. The VRC 609 study is now being conducted to evaluate a single 5 or 20 mg/kg dose of GSK3810109 (N6LS) co-mixed with rHuPH20 by SC infusion.

As of 4 August 2021, no significant safety findings were noted. GSK3810109 was generally well-tolerated, with no serious adverse events (SAEs), dose-limiting toxicities, or deaths reported.

All unsolicited events were mild or moderate in severity except for one Grade 3 diarrhea that began 4 days after administration, spontaneously resolved 2 days later, and was determined to be possibly related to GSK3810109 (N6LS). Solicited systemic symptoms were reported in 4/14 (29%) participants following IV administration and 3/12 (25%) participants following SC administration. Symptoms reported after IV administration included 4 events of mild headache, 1 mild event each of malaise, chills, and nausea. Symptoms reported after SC administration included 1 mild event each of malaise, myalgia, headache, and nausea. No fever occurred after IV or SC administration. Solicited local symptoms reported included moderate bruising (1/14 participants, 7%) following IV administration. Solicited local symptoms after SC administration included mild pain/tenderness (9/12 participants, 75%), mild to moderate swelling (4/12 participants, 33%), mild to severe redness (6/12 participants, 50%), and mild pruritus (3/12 participants, 25%).

A study pause occurred on 23 July 2021 after criteria for a pause was met due to two Grade 3 injection site erythema events not resolving during the solicited diary card reporting period. A participant after receiving 5 mg/kg SC N6LS + 2000 U rHuPH20/mL developed injection site erythema to a maximum diameter of 13 cm, which resolved after 30 days. Another participant after receiving 20 mg/kg SC N6LS + 2000 U rHuPH20/mL developed injection site erythema to a maximum of 20 cm, which resolved after 7 days. Since the episodes of Grade 3 erythema observed in both individuals were well tolerated, not accompanied by any other symptoms or laboratory abnormalities that would indicate potential systemic toxicity, and resolved without clinical sequelae, the erythema was judged to not represent an increased safety risk for study participants. Therefore, the study pause was lifted on 28 July 2021. In addition, the Protocol Safety Review Team

(PSRT) determined that the protocol would not need to be paused for future events of the same type and severity.

There is known data for GSK3810109 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 FcRn, which are similar to GSK3810109 [Gaudinski, 2018] [Gaudinski, 2019].

These other bNAbs were administered at similar doses, frequency and routes as GSK3810109 in the FTIH VRC 609 study and have been generally well-tolerated with no deaths or SAEs 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.

A detailed description of the chemistry, pharmacology, and safety of GSK3810109 is provided in the current IB [Investigator's Brochure].

2.2.2. Recombinant Human Hyaluronidase PH20 (rHuPH20)

The rHuPH20 enzyme facilitates the SC delivery of co-administered therapeutics by depolymerizing hyaluronan (HA) in the extracellular matrix of the SC tissue that normally serves to restrict bulk fluid flow. *Enhanze*™ Drug Product (EDP) is an investigational ready to use injectable drug product that contains 1 mg/mL (110,000 U/mL) rHuPH20. The rHuPH20 is the active ingredient of the commercial product *Hylenex*® recombinant (hyaluronidase human injection), which has been Food and Drug Administration (FDA)-approved since 2005 for SC fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in SC urography for improving resorption of radiopaque agents. High dose biologics previously limited to the IV route of administration due to volume, can be successfully administered SC with rHuPH20.

rHuPH20 co-administration can provide additional benefits, such as improved absorption, increased bioavailability, and reduced PK variability of certain agents [Morrow, 2011; Morcos, 2013]. Importantly, the local permeability barrier tissue changes induced by rHuPH20 are reversible within 24 to 48 hours after administration, without any inflammatory or histological changes [Locke, 2019].

As of 02 December 2021, 1,592 participants were exposed to *Hylenex* and other rHuPH20 drug products in 30 clinical studies conducted under IND 66,888 or in

post-marketing Phase 4 studies. Individual doses of rHuPH20 ranged from 15 to 96,000 U (see the current IB; [Investigator's Brochure rHuPH20]).

Across all Halozyme-sponsored studies, SC injections of rHuPH20 have been well-tolerated in healthy participants, dehydrated pediatric participants, hospice and palliative care participants, participants with type 1 and 2 diabetes, and participants with rheumatoid arthritis. The SC injections of rHuPH20 alone or in combination with hydration fluids (Lactated Ringer's, normal saline), co-injected small molecules (morphine, ceftriaxone, ondansetron), peptides (insulin, and insulin analogs), and proteins (IgG and adalimumab) have been well-tolerated in all clinical trials [Locke, 2019; Shpilberg, 2013]. Most adverse events (AEs) were mild, transient injection site reactions (ISRs), including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate ISRs, which have occurred less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported.

rHuPH20 is currently co-formulated with 4 approved anticancer therapies, trastuzumab (*Herceptin Hylecta*™/*Herceptin*® SC), pertuzumab/trastuzumab (*Phesgo*™), daratumumab (*Darzalex Faspro*™), rituximab (i.e., *Rituxan Hycela*®/*Rituxan*® SC/*Mabthera*® SC), and dosed sequentially with human immunoglobin to treat primary immunodeficiency (*HyQvia*®/*HYQVIA*®).

The specific non-clinical pharmacology, PK, and toxicity studies evaluating rHuPH20 are summarized in the rHuPH20 current IB, Section 4 [Investigator's Brochure rHuPH20].

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

2.3.1.1. Risks of GSK3810109 and MAb Administration

Typically, the side effects of monoclonal antibodies (MAbs) are mild but may include reactions at injection site (pain, redness, bruising, swelling), fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain. Up to Grade 3 injection site erythema has been observed after GSK3810109 + rHuPH20 injection, and some ISRs have lasted up to 6 weeks before completely resolving. Clinical use of MAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections (Hansel, 2010); however, this is not expected to be a risk for a MAb targeted to a viral antigen.

Administration of MAbs may cause immune reactions such as acute anaphylaxis, cytokine release syndrome, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with MAb targeted to human proteins or with the use of murine or chimeric MAbs which would have a risk of human anti-mouse antibodies (Hansel, 2010). In this regard, as GSK3810109 is expected to have a low risk of such side effects since it is directed against a viral antigen and is human in sequence origin.

Published experience with other human MAbs directed against the cell surface targets on lymphocytes have shown that infusion of an MAb may be associated with cytokine release, causing a reaction known as "cytokine release syndrome" (CRS) (Bugelski, 2009). Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia, are infrequent and more often associated with MAbs targeted to human proteins or when a non-human MAb, such as a murine MAb, is used (Hansel, 2010). Specifically, with regard to the rare CRS reactions, these generally occur within the first few hours of beginning the infusion and are more common with the first MAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the MAb and the burden of target cells is greatest at the time of the first MAb treatment. With licensed therapeutic MAbs, CRS is managed by temporarily stopping the infusion, administration of histamine blockers and restarting the infusion at a slower rate (Vogel, 2010).

Delayed allergic reactions to other MAbs may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the MAb and is noted to be more common with chimeric types of MAbs (Hansel, 2010).

There are several FDA-licensed MAbs for which reactions related to the rate of IV infusion have been described. Some symptoms may be treated by slowing or stopping the infusion. Supportive treatment or pre-medications may also be indicated for some signs and symptoms.

Other bNAbs under development for the treatment of HIV-1 that operate through the same mechanism of action as GSK3810109 (CD4 binding site) include VRC01, VRC01LS (Gaudinski, 2018) and 3BNC117. These bNAbs were well tolerated in clinical studies without clear adverse safety concerns. The predominant local reactogenicity complaint was mild pain/tenderness, although reports of mild injection site pruritus, redness, and swelling occurred at modestly higher frequencies with SC administration. Malaise, muscle pain, and headache were the most frequently reported solicited complaints noted in the 3 days post product administration. These events have been mostly mild in severity and transient. Infrequent, urticaria and infusion reactions comprising of chills, rigors, myalgia, headache, and/or fever have been reported after IV infusions. Participation in this study may limit a participant's eligibility for other future MAb studies.

2.3.1.2. Risks of EDP Co-administration

Co-administration of EDP (high concentration rHuPH20) may cause mild, transient ISRs, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate ISRs have occurred less frequently and include burning, erythema, pain, and numbness. Mild to moderate headache is also commonly reported. AEs in clinical trials have otherwise reflected the adverse reaction profiles of the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid in the SC tissue.

2.3.1.3. Risks of Blood Drawing

Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. In this study, an IV line that can be used for the collection of blood may be left in place for several hours on the days when there are frequent PK blood draws. Problems from use of an IV line for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and rarely, infection, vein irritation (called phlebitis), or blood clot.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3810109		
Serious/severe immune reactions **Anaphylaxis and 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 (anaphylaxis is a life-threatening reaction with respiratory, cardiovascular, cutaneous, or gastrointestinal manifestations), 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 MAbs, which would have a risk of human anti-mouse antibodies. Cytokine release syndrome reactions most commonly occur within the first few hours of beginning the infusion and are more 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. GSK3810109 is expected to have a low risk for serious/severe immune reactions as it is directed against a viral antigen and is human in sequence origin. No	Vital signs will be monitored and prompt treatment of anaphylaxis is critical, with SC or intramuscular epinephrine and IV 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. Urinary and serum histamine levels and plasma tryptase levels drawn after onset of symptoms may assist in diagnosis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	serious/severe immune reactions have been previously observed with GSK3810109.	
Local reactogenicity (ISRs)	**Non-clinical** The repeat dose IV and SC administration of GSK3810109 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** In Study VRC 609 as of 04 August 2021, solicited local symptoms reported included moderate bruising (1/14 participants, 7%) following IV administration. Solicited local symptoms after SC administration included mild pain/tenderness (9/12 participants, 75%), mild to moderate swelling (4/12 participants, 33%), mild to severe redness 6/12 participants, 50%), and mild pruritus (3/12 participants, 25%).	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), or tattoos 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 ISRs. Advice on care, monitoring, natural course, and treatment of ISRs given in study documentation. Advice to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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.
Systemic reactogenicity	**Non-clinical** In the repeat-dose study in Sprague Dawley rats of 3 weeks' duration, 2 females given 40 mg/kg/IV showed hypoactivity and prostrate posture on Day 21 immediately and/or 2 to 4 hours post dose with recovery within 24 hours, consistent with an infusion-related reaction. **Clinical** The solicited systemic symptoms were reported in 4/14 (29%) participants following IV administration and 3/12 (25%) participants following SC administration. Symptoms reported after IV administration included 4 events of mild headache, 1 mild event each of malaise, chills, and nausea. Symptoms reported after SC administration included 1 mild event each of malaise, myalgia, headache, and nausea. No	Participants will be closely monitored for local (appearance of symptoms)/systemic reactions. IV access will be placed in an arm vein in an aseptic manner. GSK3810109 will be diluted with normal saline to infuse approximately 250 mL of solution at the appropriate concentration over approximately 60 minutes but not to exceed 2 hours. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms. Supportive treatment or pre-medications may be indicated for some signs and symptoms. Vital signs and SPO_2 will be monitored during IV infusions

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	fever occurred after IV or SC administration. 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.	
Gastrointestinal disorders **(Diarrhea)**	**Non-clinical** Not applicable **Clinical** In the Phase 1 study, 3 participants experienced diarrhea (Grade 1 to 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 gastrointestinal AEs 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.
Liver chemistry elevations	**Non-clinical** The repeat-dose IV and SC administration of GSK3810109 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 AST, ALT and/or ALP, correlating with the histopathologic findings in the liver, within high-end of normal ranges and considered not to	Participants with liver impairment based on screening liver chemistry will be excluded: Participants with ALT> × 1.5 ULN or total bilirubin >1.5 × ULN are excluded (Exclusion criteria #16 and #17). Liver aminotransferases (ALT and AST) will be monitored throughout this study (refer to SoA,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have reached a level of toxicity. **Clinical** A total of 3 (14%) participants experienced transient Grade 1 or 2 liver enzyme elevations (2 ALT elevation; 1 AST elevation).	Section1.5, Section 1.6, and Section 1.7) and the liver chemistry stopping criteria will be adopted as described in Section 10.5 of this protocol. Liver chemistry stopping criteria: • ALT≥3 × ULN • If ALT≥3 × ULN AND bilirubin ≥2 × ULN (>35% direct bilirubin) or INR >1.5, i.e., Hy's case, report event as an SAE.
Neutropenia	**Non-clinical** The repeat-dose IV and SC administration of GSK3810109 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. **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 × 10^3 cells/μL.	Close monitoring of blood counts in participants initiating therapy will be conducted throughout this study (refer to SoA, Section 1.5, Section 1.6, and Section 1.7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Neutropenia (0.75×10^3 cells/μL) started 23 days post dose (single IV dose; 20 mg/kg) and returned to 3.11×10^3 cells/μL (within normal range) 13 days later at the next specimen collection. No intercurrent illness or confounding concomitant medication was reported.	
Immunogenicity	**Non-clinical** GSK3810109 exhibited lower serum concentrations after repeat administration via both routes in the dose ranges studied suggesting the formation of CCI 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, 2 females given 40 mg/kg/IV showed hypoactivity and prostrate posture on Day 21 immediately and/or 2 to 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 CCI 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	The emergence of CCI will be actively monitored using a validated CCI (screening, confirmation, and titration).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	humans. There were CCI detected in 2/22 (9%) of GSK3810109-treated participants at any time after dosing, however, no neutralizing activity was exhibited. There were no discernible effects of immunogenicity on the safety and PK profiles from the Phase 1 study.	

CCI AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; INR = international normalized ratio; ISR = injection site reaction; IV = intravenous; MAb = monoclonal antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; SoA = schedule of activities; ULN = upper limit of normal.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Recombinant Human Hyaluronidase PH20 (rHuPH20)		
Spread of localized infection	rHuPH20 should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection.	Training will be provided to relevant staff regarding proper injection technique.
Hypersensitivity	Hypersensitivity, allergic, and anaphylactic-like reactions have been associated with animal-derived hyaluronidases but have not been associated with rHuPH20.	Participants with a history of hypersensitivity to hyaluronidases are excluded.
Inadvertent IV administration	In a study of healthy volunteers administered 10,000 U or CCI of rHuPH20 intravenously, rHuPH20 had a half-life of less than 10 minutes and was well tolerated. There were no associated serious adverse effects (Investigator's Brochure rHuPH20).	Training will be provided to relevant staff regarding proper injection technique. No mitigation activities are needed if there is suspected IV administration of rHuPH20.
Injection Site Reactions (ISRs)	rHuPH20 may cause ISRs. These ISRs are mostly mild, transient ISRs, including erythema, pain,	Participants will be closely monitored for throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Recombinant Human Hyaluronidase PH20 (rHuPH20)		
(Applicable only for Part 1 and Part 3)	bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate ISRs occur less frequently, include burning, erythema, pain, and numbness (Investigator's Brochure rHuPH20). rHuPH20 may potentially alter the ISR profile of GSK3810109.	Significant ISRs will be photographed and referred to a dermatologist for specialist advice and possible biopsy. Most AEs reported in clinical trials with rHuPH20 were mild, transient ISRs, including erythema. It is currently unknown if rHuPH20 may impact the ISR profile of GSK3810109.

2.3.2. Benefit Assessment

There are no direct benefits to study participants from study participation. Others may benefit from knowledge gained in this study that may aid in the development of HIV risk-reduction or therapeutic methods.

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 for SC and IV administration (refer to Section 4.3), the overall risk to healthy participants in this study is predicted to be low and manageable.

3. OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single dose of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants	**Part 1 and Part 3 (SC injection)** • The number and percentages of participants who have AEs (Grade 2 or higher) and SAEs following GSK3810109 SC administration through Week 24 • The number and percentages of participants who have ISRs within 7 days following GSK3810109 SC administration • The incidence of Grade 2 to 4 elevated ALT/AST following GSK3810109 SC administration **Part 2 (IV infusion)** • The number and percentages of participants who have AEs and SAEs following GSK3810109 IV administration through Week 24 • The incidence of Grade 2 to 4 elevated ALT/AST following GSK3810109 IV administration through Week 24
Secondary	
• To evaluate the PK of a single dose of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants	• Assessment of GSK3810109 PK parameters including AUC(0-inf), AUC(0-t), Cmax, Tmax, and t1/2 (if possible)
• To assess the severity and acceptance of pain and ISRs after SC administration of GSK3810109 with rHuPH20	• Dimension score “acceptance of ISRs” and individual item score assessing pain at Day 2 and Day 7 using the PIN Questionnaire • Proportion of participants who are bothered or affected by the pain and local reactions as a result of the injection as measured by the PIN on Days 2 and 7

Objectives	Endpoints
	• Post-injection pain assessment using NRS at Days, 1, 2, and 7 • The incidence and duration of ISRs assessed overall and by grade including the duration at grade
• To assess the severity of pain after IV administration of GSK3810109	• Post-infusion pain assessment using NRS at Days, 1, 2, and 7
• To evaluate additional safety parameters following administration of GSK3810109 SC with rHuPH20 or IV in healthy adult participants	• Change from baseline in clinical laboratory assessments, ECGs, and vital sign measurements
Exploratory	
CCI [redacted]	

CCI [redacted]; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC(0-inf) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0 t) = area under the plasma concentration-time curve from time zero to time of last observed quantifiable concentration; Cmax = maximum observed concentration; ECG = electrocardiogram; ISR = injection site reaction; IV = intravenous (ly); NRS = Numeric Rating Scale; PIN = Perception of Injection; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous (ly); t1/2 = apparent terminal phase half-life; Tmax = time of maximum observed concentration

Primary estimand

The primary questions of interest are: What is the safety and tolerability of a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20 or a single 60 mg/kg IV dose of GSK3810109 or CCI [redacted]?

The primary safety estimands are described by the following attributes:

- Population: Healthy male and female participants aged 18 to 65 years of age, inclusive.
- Treatment conditions:
  - Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20.
  - Part 2: Single 60 mg/kg IV dose of GSK3810109.
  - CCI [redacted]
- Variables:
  - Part 1 and Part 3: Incidence of AEs (Grade 2 or higher) and SAEs through Week 24, incidence of ISRs within 7 days of GSK3810109 administration, and incidence of Grade 2 to 4 elevated alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) values.
  - Part 2: Incidence of AEs and SAEs through Week 24 and incidence of Grade 2 to 4 elevated ALT/AST values.
- Summary measures:
  - Part 1 and Part 3: Number and percentage of participants reporting AEs (Grade 2 or higher) or SAEs through Week 24; number and percentage of participants reporting ISRs within 7 days of GSK3810109 administration; number and percentage of participants with Grade 2 to 4 elevated ALT/AST.
  - Part 2: Number and percentage of participants reporting AEs or SAEs through Week 24; number and percentage of participants with Grade 2 to 4 elevated ALT/AST.
- Intercurrent events (Part 1, Part 2, and Part 3):
  - Discontinuation from study for any reason: Treatment policy strategy will be applied to address this intercurrent event, as safety data will be collected at the follow-up visit and will be reported for all participants
- Rationale for Estimands: Interest lies in the safety and tolerability for a participant receiving either a single SC dose of GSK3810109 co-administered with rHuPH20 or a single IV dose of GSK3810109.

Secondary estimands

The secondary PK questions of interest are: What is the PK profile of a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20, or a single 60 mg/kg IV dose of GSK3810109, or CCI [redacted]?

These secondary PK estimands are described by the following attributes:

- Population: Healthy male and female participants aged 18 to 65 years of age, inclusive.
- Treatment conditions:
  - Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20.
  - Part 2: Single 60 mg/kg IV dose of GSK3810109.
  - CCI [redacted]
- Variables (Part 1, Part 2, and Part 3):
  - Assessment of GSK3810109 PK parameters: AUC(0-inf), AUC(0-t), Cmax, Tmax, and t1/2
- Summary measures (Part 1, Part 2, and Part 3):
  - Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) will be summarized.
- Intercurrent events (Part 1, Part 2, and Part 3):
  - Discontinuation from study for any reason: While-on treatment strategy will be applied to address this intercurrent event. (Only on-treatment PK data prior to the intercurrent event is of interest for the secondary PK estimands).

Additional secondary questions of interest are: Part 1: What is the severity and acceptance of pain and ISRs after a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20 in healthy adults? Part 2: What is the severity of pain after a single 60 mg/kg IV dose of GSK3810109 in healthy adults? CCI [redacted]

These secondary severity and acceptance estimands are described by the following attributes:

- Population: Healthy male and female participants aged 18 to 65 years of age, inclusive.
- Treatment conditions:
  - Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20.
  - Part 2: a single 60 mg/kg IV dose of GSK3810109.
  - CCI [redacted]

- Variables:

Part 1 and Part 3:

- Dimension score and individual item score assessing pain at Day 2 and Day 7 from the Perception of Injection (PIN) Questionnaire; following injection, incidence of pain and local reactions where participants reported being bothered or affected using the PIN Questionnaire on Day 2 and Day 7; numeric rating scale (NRS) pain assessment scores following injection at Days 1, 2 and 7; and incidence and duration of ISRs and duration of grade of ISRs.

Part 2:

- Numeric rating scale (NRS) pain assessment scores following infusion, at Days 1, 2 and 7.

- Summary measures:

Part 1 and Part 3:

- Summary statistics for dimension score "acceptance of ISRs" and individual item score assessing pain on Day 2 and Day 7 using PIN Questionnaire; number and percentage of participants reporting they were bothered or affected by the pain and local reactions based on the PIN Questionnaire; summary statistics of post-injection pain assessment scores based on the NRS at Days 1, 2, and 7; number and percentage of participants for each pain assessment score from 0 to 10 (0: CCI 10: CCI); number and percentage of participants reporting ISRs overall and by grade. Summary statistics of the duration of the ISRs overall and by grade.

Part 2:

- Summary statistics of post-infusion pain assessment scores based on the NRS at Days 1, 2, and 7. Number and percentage of participants for each pain assessment score from 0 to 10 (0: CCI , 10: CCI).

- Intercurrent events (Part 1, Part 2, and Part 3):

- Discontinuation from study for any reason: Treatment policy strategy will be applied to address this intercurrent event, as safety data will be collected at the follow-up visit and will be reported for all participants.

Additional secondary questions of interest are: Part 1: What is the safety (based on additional secondary safety parameters) of a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20 in healthy adults? Part 2: What is the safety (based on additional secondary safety parameters) of a single 60 mg/kg IV dose of GSK3810109 in healthy adults? Part 3: CCI

These secondary safety estimands are described by the following attributes:

Population: Healthy male and female participants aged 18 to 65 years of age, inclusive.

- Treatment conditions:
  - Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20.
  - Part 2: Single 60 mg/kg IV dose of GSK3810109.
  - CCI [redacted]
- Variables (Part 1, Part 2, and Part 3):
  - Change from baseline in laboratory assessments, ECGs, and vital sign measurements.
- Summary measures (Part 1, Part 2 and Part 3):
  - Summary statistics for change from baseline in clinical laboratory assessments, electrocardiograms (ECGs) and vital sign measurements.
- Intercurrent events (Part 1, Part 2, and Part 3):
  - Discontinuation from study for any reason: Treatment policy strategy will be applied to address this intercurrent event, as safety data will be collected at the follow-up visit and will be reported for all participants.

Exploratory estimands

CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-dose study to assess the safety, tolerability, and PK of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants.

This study will comprise 3 parts:

In Part 1, approximately 8 participants will receive a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20 at dose of 2000 U/mL or ~28,000 U for a 70 kg participant. The participants will be admitted in the clinic on Day –1 and the study product will be administered on Day 1. The participants will remain in the clinic for approximately 8 hours for study-related procedures after study product administration and will be followed up for 24 weeks.

Safety laboratory samples will be collected throughout the study as per the SoA. The primary endpoint of ISR will be evaluated at specified time points up to Day 7; study participants will keep a diary of ISRs for 14 days after study product administration. Symptoms, maximum intensities, and durations will be reported through end of study to characterize presentation and resolution of local ISRs.

Safety review decisions and the status of the enrollment process will be shared with the Safety Review Team (SRT) in regular intervals and discussed during the monthly SRT meetings.

In Part 2, approximately 8 participants will receive a single 60 mg/kg IV dose of GSK3810109. A sentinel cohort of 2 participants will be used to mitigate the risk of unexpected AEs prior to dosing of the remaining 6 participants, who will be dosed in sequential cohorts of 2 participants each.

The sentinel cohort of these 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks.

Following Day 10 visit, core SRT will review the safety data (safety laboratory data, ECG, and AEs) from the sentinel cohort and may recommend continuation of the study where the next cohort of 2 participants will be dosed.

The second cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks. A review of at least AE data from this cohort will be conducted after a minimum of 4 days following infusion of GSK3810109 and the core SRT may recommend continuation of the study where the next cohort of 2 participants will be dosed.

The third cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks. A review of at least AE data from this cohort will be conducted after a minimum of 4 days following infusion of GSK3810109 and the core SRT may recommend continuation of the study into the fourth cohort of 2 participants.

The fourth cohort of 2 participants will be admitted to the clinic on Day –1. The study product will be administered on Day 1 and participants will remain in the clinic and be monitored for 7 days after study product administration. The participants will be discharged from the clinic on Day 8 and will be followed up for 24 weeks.

Safety laboratory samples will be collected throughout the study as per the SoA.

CCI

4.2. Scientific Rationale for Study Design

GSK3810109 is a human MAb active against HIV that can mediate extraordinary breadth and potency against various HIV isolates, including strains traditionally resistant to other antibodies in this class.

This study is designed to evaluate safety, tolerability, and PK endpoints in healthy adult participants, when GSK3810109 is administered as either SC injection (Part 1 and Part 3 of study) or IV infusion (Part 2 of study). The inclusion of both routes of administration in this study is an efficient design to enable rapid progression to future studies using either 1 or both routes of administration.

The potency of GSK3810109 may indicate fewer antibodies are required to mediate an effect, offering the possibility of SC administration as a more feasible approach to immunoprophylaxis. The introduction of the leucine serine (LS) site-directed mutation to increase FcRn binding affinity is postulated to result in increased antibody half-life and persistence at biologically higher concentrations in the plasma, as was shown for VRC01LS and VRC07-523LS (Rudicell, 2014; Ko, 2014; Gaudinski, 2018).

The rHuPH20 enzyme facilitates SC delivery of co-administered therapeutics. The use of rHuPH20 with GSK3810109 offers the potential to administer a larger volume of the antibody than could be administered alone (~2.0 mL). Therefore, the current study will investigate the ability to deliver a larger SC dose of GSK3810109 (20 mg/kg, up to 24 mL) in combination with rHuPH20. The rHuPH20 will be co-mixed with GSK3810109 at a concentration of 2000 U/mL based on the dosing volume of GSK3810109.

In clinical studies to date for SC doses of rHuPH20 up to 30,000 U, systemic exposure has been undetectable Kirschbrown, 2018. CCI [redacted]

There is a practical limitation for administration of high doses of GSK3810109 via SC infusion. To date, the maximum dose administered via SC route is 20 mg/kg, in combination with rHuPH20, while an IV route allows higher dose administration. In this study, an IV dose of 60 mg/kg of GSK3810109 will be administered, which offers the potential for an ultra-long-acting target profile to support administration every 4 to 6 months, thus reducing dosing frequency and potentially improving adherence and acceptability. Medication adherence and decreasing frequency of clinic visits is the most important determinant for sustained viral suppression and long-term treatment success.

This study is participant to the appropriate regulatory and ethics committee (EC) approval and will be listed on the website ClinicalTrials.gov. No blinding or placebo control will be used, as these are not necessary for the purposes of this study.

4.3. Justification for Dose

This study will evaluate the safety and tolerability of a single SC [redacted] or IV dose of GSK3810109

Part 1

The dosages selected for evaluation of GSK3810109 are based on prior experience with another CD4-binding site antibody VRC01, which was shown in 2 clinical trials (VRC 601 and VRC 602 [Ledgerwood, 2015; Lynch, 2015]) to be safe and well-tolerated at 5 to 40 mg/kg dosages given IV and at a 5 mg/kg dosage given SC in both HIV-infected and -uninfected adult populations. From prior experience in a FTIH study (VRC 609), GSK3810109 is also shown to be well-tolerated as a single dose at 5 mg/kg, 20 mg/kg, 40 mg/kg IV, or 5 mg/kg SC and 5 mg/kg SC or 20 mg/kg IV by repeat dosing every 12 weeks for a total of 3 injections/infusions.

The VRC 609 study is now being conducted to evaluate a single 5 or 20 mg/kg dose of GSK3810109 (N6LS) co-mixed with rHuPH20 by SC infusion. As of 4 August 2021, no significant safety findings were noted. GSK3810109 was generally well tolerated, with no SAEs, dose-limiting toxicities, or deaths reported. The dose administered in this Part of the study will not exceed that in the FTIH study (VRC 609).

The 20 mg/kg dose to be administered in the current study is based on the feasibility of delivering a SC dose with rHuPH20 within approximately 3 to 15 minutes via an infusion pump, as well as a comprehensive assessment of ISRs and acceptability of drug administration. The 20 mg/kg SC dose was chosen based the volume of administration, PK, and the safety data of repeat-dosing of 20 mg/kg IV administration which supports a possible SC 12-week dosing interval in combination with other antiretroviral agents to maintain viral suppression. A 12-week interval for repeat-dosing has also been used in clinical trials with IV administration of VRC01LS and VRC07-523LS.

Part 2

GSK3810109 belongs to the VRC01 class of CD4 binding site-directed bNAbs, which block HIV infection by occluding the binding site for the cellular receptor CD4. The N6 antibody was modified by site-directed mutagenesis to increase its binding affinity for the FcRn to extend its half-life and is designated GSK3810109.

The overall compartmental half-life (t1/2β) of GSK3810109 is currently estimated to be 44 ± 6 days for IV administration and offers the potential for an ultra-long-acting target profile. Ultra-long-acting ART, defined as 3 to 6 months or longer, can help to improve treatment adherence, which is the most important determinant for sustained viral suppression, a decrease in the frequency of clinic visits, and reduction in the social stigma associated with daily therapy. Based on PK estimates from the VRC 609 study and the antiviral effect of GSK3810109 at 280 mg in HIV viremic individuals in Study 207959 (BANNER), it is estimated that a 40 mg/kg IV dosing may be able to provide coverage for 4 months but is unlikely to provide sufficient therapeutic breadth for a 6-month

dosing interval. Pharmacokinetic modelling suggests GSK3810109 given at 60 mg/kg may be adequate for every 6 months administration.

A 60 mg/kg dose of GSK3810109 will exceed the 40 mg/kg no-observed-adverse-effect level (NOAEL) set by ViiV Healthcare. The NOAEL set by the VRC is at 400 mg/kg IV and has been endorsed by the FDA. Based on the same VRC generated data, ViiV set the NOAEL at 40 mg/kg due to the morbidity of 1 male rat at 400 mg/kg, for which it was not possible to exclude a relationship to exposure. A review of observed GSK3810109 Cmax and area under the plasma concentration-time curve (AUC) exposure in humans at 40 mg/kg IV found levels to be appreciably higher than rodent exposures at the 40 mg/kg NOAEL and raises questions of the relevancy of the rodent model PK as a basis for lowering the NOAEL from 400 mg/kg to 40 mg/kg. In addition, simulated PopPK modeling shows that 60 mg/kg IV in humans is predicted to have a lower Cmax than the VRC 400 mg/kg rat NOAEL Cmax. This model was used to simulate GSK3810109 serum concentrations of 60 mg/kg IV dosing in a population of adults with a range of bodyweights representative of the anticipated volunteer population for Study 217901. Predicted individual serum concentration versus time profiles predict that after a 60 mg/kg dose, serum concentrations of GSK3810109 in all individuals will be below the average Cmax from 40 mg/kg dosing within 3 days (i.e., 72 hours) of study product administration.

No toxicologically relevant off-target binding was noted in tissue cross reactivity evaluation of adult human or rat tissues, and no staining was observed in any of the selected human neonatal tissues examined. Off-target safety review was performed by GSK using published scientific literature and a range of in silico tools; liver proliferation and increased mitochondria transmembrane potential were identified as theoretical risks for galectin-1 modulation. There were no indications of liver proliferation or mitochondria dysfunction in a repeat dose toxicology study where rats were given GSK3810109 on 3 occasions, 1 week apart up to 400 mg/kg IV.

Based on these overall findings, dose escalation of GSK3810109 to 60 mg/kg IV could be acceptable with careful risk mitigation strategies.

Safety data of human administration of GSK3810109 have found it to be safe. As of 09 March 2022, GSK3810109 has been administered by IV or SC infusion/injection to 38 HIV-uninfected adults and 14 treatment naïve HIV-infected adults and complete safety information is available in 36 participants. In all current studies, GSK3810109 has been found to be safe with no SAEs or deaths reported. All available clinical safety data relating to CD4 binding site class bNAbs and PK modelling data provide justification to conduct a Phase 1 study evaluating the safety and PK profile of IV 60 mg/kg dosing in HIV-uninfected adults.

CCI

[redacted]

CCI

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.5 , Section 1.6, and Section 1.7) for the last participant in the study.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and without history of any of the conditions listed in the exclusion criteria.

Weight

3. Body weight must be ≥50 kg and <100 kg.

Sex and Contraceptive/Barrier Requirements

4. 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.

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 agree to use contraceptive method as described in Section 10.4 from 3 weeks prior to the start of this study and during the study. 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 10.4) serum pregnancy test on Day –1, prior to the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 1.5 , Section 1.6, and Section 1.7.
- All participants in the study should be counseled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom).
- 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 10.4.2 and Section 10.4.3, respectively.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusions

6. Participants must have results that do not show clinically significant abnormalities, as judged by the investigator at screening.

5.2. Exclusion Criteria

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

Medical Conditions

1. Hypertension that is not well controlled as per investigator's discretion.
2. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data.
3. Positive HIV and/or hepatitis C antibody test
4. Positive test result for SARS-CoV-2
5. Evidence of hepatitis B virus infection at screening or within 3 months prior to first dose of study intervention
    - Participants positive for hepatitis B surface antigen (HBsAg) are excluded.
    - Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for hepatitis B virus (HBV) DNA are 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.
6. Any history of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis within the 2 years prior to enrollment that has a reasonable risk of recurrence during the study.
7. The participant has an underlying skin disease or disorder (i.e., infection, inflammation, dermatitis, eczema, drug rash, drug allergy, psoriasis, food allergy, urticaria) or tattoos that would interfere with assessment of injection sites.
8. 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.
9. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A, dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

Prior/Concomitant Therapy

10. Exposure to an experimental drug, human blood product, or vaccine (which does not have emergency, conditional, or standard market authorization) within 28 days

prior to the first dose of study treatment OR plans to receive live vaccines during the study

Note: Consult with the Medical Monitor if clarification is needed. Receipt of a Coronavirus disease 2019 (COVID-19) vaccine that has received emergency, conditional, or standard market authorization is allowed if the investigator determines that the benefit-risk profile for that individual study participant is favorable. The use of other investigational COVID-19 vaccines that have not received emergency, conditional, or standard market authorization and are still only used in clinical trials will not be allowed at this time.

Prior/Concurrent Clinical Study Experience

11. Prior receipt of licensed or investigational MAb.
12. Receipt of any investigational study agent within 28 days prior to first dose of study treatment
13. Prior exposure to GSK3810109 or rHuPH20 in this or another clinical study.
14. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.

Diagnostic Assessments

16. Alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal (ULN).
17. Total bilirubin ≥1.5 times the ULN (isolated total bilirubin >1.5×ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).
18. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
19. QTcF >450 msec for males and QTcF >470 msec for females.

    NOTES:

    - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF) machine-read or manually over-read.
    - QTcF will be used to determine eligibility and stopping/pause criteria for an individual participant in this study.
20. The participant has a tattoo or other dermatological condition overlying potential injection sites that may interfere with interpretation of ISRs or administration of GSK3810109
21. Grade 4 laboratory abnormalities

Other Exclusions

22. Any other chronic or clinically significant medical condition that in the opinion of investigator would jeopardize the safety or rights of the participant including (but not limited to): diabetes mellitus type I, chronic hepatitis; OR clinically significant forms of drug or alcohol abuse, asthma, autoimmune disease, psychiatric disorders, heart disease, or cancer.
23. Known hypersensitivity to hyaluronidase or any of the excipients in EDP.

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, Alcohol, and Tobacco

- There are no study-related restrictions on caffeine and tobacco.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing through Day 1.

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

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

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

5.5. Criteria for Temporarily Delaying

Not applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1. Study Interventions Administered

Table 1 Study Interventions Administered

Intervention Label		
Intervention on Label	GSK3810109	rHuPH20
Intervention Description	GSK3810109 is a clear, colorless to yellow liquid that is essentially free of visible particles; the product is supplied as a sterile aqueous buffered solution filled into 10 mL single-dose vials.	Each vial of ENHANZE™ Drug Product (EDP) contains 0.5 mL of rHuPH20 formulated at a concentration of 1 mg/mL (~110,000 U/mL rHuPH20). EDP is manufactured by Ajinomoto Althea, Inc, (San Diego, CA) for Halozyme Therapeutics, Inc. (San Diego, CA) and is supplied in 2 mL glass vials as a sterile, single-dose, injectable liquid.
Type	Biologic	Biologic
Dose Formulation	Vial	Vial
Unit Dose Strength	600 mg/6mL vial	Each vial of EDP contains 0.5 mL of rHuPH20 formulated at a concentration of 1 mg/mL (~110,000 U/mL rHuPH20)
Dosage Level	For Part 1, SC infusion 20 mg/kg For Part 2, IV infusion 60 mg/kg CCI [redacted]	2000 U/mL based on dose of GSK3810109
Route of Administration	SC infusion/IV infusion	SC infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP

Intervention Label		
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.
Current/Former Name or Alias	GSK3810109 /VH3810109/ N6LS	*Enhanze*™ Drug Product (EDP)

EDP = ENHANZETM Drug Product; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product.; SC = subcutaneous.

6.2. Study Product Administration

Subcutaneous Administration with rHuPH20

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. GSK3810109 will be mixed with rHuPH20 in the pharmacy and then administered via standard Medfusion 3500 syringe pump (or equivalent) in 1 infusion site at a rate of no more than 3 mL/minute. For Part 1, given the weight criterion in this study, the maximum volume needed to administer a 20 mg/kg SC dose is not expected to exceed 24 mL. CCI [redacted]. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

Intravenous Administration

For Part 2, participants will receive IV administration of GSK3810109. The IV access will be placed in an arm vein in an aseptic manner. A different site should 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. GSK3810109 will be diluted with normal saline to infuse approximately 250 mL of solution at the appropriate concentration (as described in the current IB [Investigator's Brochure]) over about 60 minutes. The entire infusion should not exceed 2 hours. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or interrupted to alleviate the symptoms.

There are no pre-medications for IV administration; however, based on emerging safety data from sentinel participants, these may be given at the investigator's discretion and in consultation with the Medical Monitor.

Study Product and Administration Regimen

GSK3810109 is a clear, colorless to yellow liquid, that is essentially free of visible particles; the product is supplied as a sterile aqueous buffered solution filled into 10 mL single-dose vials. Each vial contains a 6.25 ± 0.10 mL volume of GSK3810109 at a concentration of 100 ± 10 mg/mL in a formulation buffer composed of 10 mM sodium citrate, 50 mM sodium chloride, 150 mM arginine-hydrochloride, and 0.002%

polysorbate-80 at pH 6.5. Vials have a nominal fill volume of 6.25 mL to enable withdrawal up to 6.0 mL.

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 at least 6 mL can be withdrawn from a vial. In this study, dose is limited or established based on participant weight. For example, for a participant weighing 100 kg (the upper limit per protocol eligibility) who receives a 20 mg/kg dose, the GSK3810109 amount needed is calculated as follows: 100 kg × 20 mg/kg = 2000 mg of GSK3810109, which corresponds to 20 mL of the 100 mg/mL solution. Since each product vial contains at least 6 mL, 4 vials will be needed for the dose preparation for this participant.

Refer to Pharmacy Manual for specific handling, preparation, and administration instructions.

6.3. Preparation, Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor, and/or ViiV/GSK study contact.

A Material Safety Data Sheet/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 ViiV/GSK.

The detailed guidance and information on preparation, handling, storage, and accountability is provided in the Study Reference Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Study product will be administered sequentially to the participants in Part 2 and Part 3 (Section 4.1 and Section 1.6, and Section 1.7).

6.5. Study Intervention Compliance

GSK3810109 will be administered to participants either SC with rHuPH20 or IV at the study site. Administration will be documented in the source documents and reported in the electronic case report form (eCRF)

6.6. Overdose

For this study, any administered dose of GSK3810109 and/or rHuPH20, greater than that intended for the study will be considered an overdose.

The investigator should use clinical judgment 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 GSK3810109 can no longer be detected systemically.
4. Obtain a 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 eCRF.

Since this is a single-dose administration of GSK3810109, dose modifications will not be applicable. However, if the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

6.7. 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. All concomitant medications, blood products, and vaccines (clinicians should work with participants regarding the timing of licensed vaccines relative to study product administration) taken during the study will be recorded in the eCRF with dates of administration.

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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Emerging safety data will be reviewed in-stream as the study progresses and the following criteria will result in a study pause. A full safety review will be conducted, and the findings and recommendations presented to ViiV Safety and Labelling Committee (VSLC) for endorsement:

- Any SAE, regardless of its severity, that is considered be clinically significant and reasonably attributable to dosing with GSK3810109, in the opinion of the investigator and sponsor.
- Acute allergic reaction or CRS (Division of AIDS [DAIDS] criteria Grade 3 to 4) reasonably attributable to dosing with GSK3810109, in the opinion of the investigator and sponsor.
- Any AE of Grade 4 intensity assessed as related to GSK3810109, as reported by the investigator.
- Any participant meeting liver chemistry stopping criteria (see Section 7.2)
- Any participant meeting QTcF stopping criteria (see Section 7.3)
- If 2 participants in any discrete part of the study (Part 1, Part 2, or Part 3) experience an AE of Grade 3 intensity (excluding ISRs) assessed as related by the investigator.
- If 2 or more injections/infusions administered in any discrete part of the study (Part 1, Part 2, or Part 3) are followed by an ISR of at least Grade 3 in severity.

  Note: Grade 3 ISRs that are based on the size of erythema or induration alone will not be considered as a pausing criterion. However, any Grade 3 ISR of erythema or induration due to ulceration, secondary infection, phlebitis, sterile abscess, drainage, or symptoms causing inability to perform usual social and functional activities (as per DAIDS) will be included as a pausing criterion.

Relevant reporting and discussion with the Medical Monitor, relevant study team personnel, and the institutional review board (IRB)/independent ethics committee (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.

7.2. 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 pre-marketing clinical liver safety guidance [DHHS, 2009]).

Discontinuation of GSK3810109 is not possible for abnormal liver tests as this is a single-dose study. 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.

Liver Chemistry Stopping Criteria

- ALT ≥3 × ULN
- If ALT ≥3 × ULN AND bilirubin ≥2 × ULN (>35% direct bilirubin) or international normalized ration >1.5, report as an SAE.

Refer to Section 10.5 for required Liver Safety Actions and Follow up Assessments.

7.3. QTcF Stopping Criteria

If a participant meets the below mentioned QTcF 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.

QTcF Stopping Criteria:

- QTcF > 480 msec,
- Change from baseline: QTcF >60 msec

7.4. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.5. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible 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 1.5, Section 1.6, and Section 1.7).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (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 timeframe defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

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

8.1. Safety Assessments

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

8.1.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will include at minimum, assessment of skin, lungs, cardiovascular system, and abdomen [liver and spleen]). For Part 2, a brief physical examination will also be performed within 30 to 60 minutes of end of infusion (EOI).
- 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.

8.1.2. Vital Signs

- Vital signs will be measured in a supine position after the participant has been at rest for at least 5 minutes in a quiet setting without distractions (e.g., television, cell phones) and will include body temperature, systolic and diastolic blood pressure, respiratory rate, and pulse.
- For Part 1, on Day 1, the vital signs and SPO_2 will be measured at predose and at 4 hours and 8 hours postdose.
- For Part 2, on Day 1, the vital signs and SPO_2 will be measured at predose, every 15 minutes from start of infusion for 2 hours, and at 4 hours and 8 hours postdose.
- For Part 3, on Day 1, the vital signs and SPO_2 will be measured at predose and at 4 hours and 8 hours postdose.

8.1.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained in a supine position as outlined in the SoA (Section Section 1.5, Section 1.6 and Section 1.7) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. The ECG taken at Screening and on Day 1 before study product administration will be a single reading; however, repeat ECGs are allowed at investigator's discretion to confirm the eligibility. Triplicate 12-lead ECG will be obtained for all postdose time points. For Part 2, for Visit 01A, ECGs will be taken within 30 minutes of EOI.

- The ECG should be read locally and be centrally archived. Please contact the Medical Monitor if any concerns.

8.1.4. Clinical Safety Laboratory Tests

- Refer to Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.5, Section 1.6 and Section 1.7) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. 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 Section 10.2 must be conducted in accordance with the laboratory manual and the SoA (Section 1.5, Section 1.6 and Section 1.7), through the central laboratory.

8.1.5. Pregnancy Testing

- 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 ViiV/GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.3.

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

8.1.6. COVID-19 Measures

The measures approved for implementation within this clinical study to protect participant safety, welfare, and rights, and to ensure data integrity and the integrity of the clinical study, as a result of COVID-19 only, are outlined in Section 10.6.

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

The definitions of an AE or SAE can be found in Section 10.3. As described in Appendix 3 (Section 10.3) intensity of AEs (and laboratory abnormalities) will be graded using the 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 AEs related to COVID-19, please see Section 10.6.5.2.

8.2.1. 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 1.5 , Section 1.6, and Section 1.7). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK product will be recorded from the time a participant consents to 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 1.5 ,Section 1.6, and Section 1.7).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF 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 10.3.4. 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.

8.2.2. Method of Detecting AEs and SAEs

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

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, 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 7.5). Further information on follow-up procedures is given in Section 10.3.3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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, IRB/ IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5. 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 will record pregnancy information on the appropriate form and submit it to ViiV/GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on

the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.2.6. Adverse Events of Special Interest

Adverse events of special interest include: ISRs (only for Part 1 and Part 3), infusion-related reactions, and serious/severe immune reactions (including anaphylaxis and CRS).

8.2.7. Specific Toxicities/Adverse Event Management

8.2.7.1. Injection/ Infusion Site Reactions (ISRs)

All ISRs will be graded using the DAIDS grading table. 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 7 days must be discussed with the Medical Monitor to determine etiology and assess appropriate continued study participation.

Digital photographs will be documented in all participants who have an ISR. Dermatology may be consulted for all participants who have an ISR 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. Grade 3 ISR consisting of erythema alone will not require dermatology consultation, but will be at the discretion of the investigator.

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

Injection/infusion site erythema or swelling will be evaluated and graded using the measured surface area (using the calculation of diameter/2 × length/2 × Pi [3.14]) and data regarding the size of these ISRs recorded at each ISR measurement (width and length).

Injection/infusion site reaction 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.

For Part-2, infusion site reaction will be collected in the form of AE only.

Diary Cards (applicable to only Part 1 and Part 3)

Participants will complete a diary card following GSK3810109 injection. This allows participants to record and score the severity of any reactions, record the impact of the injection on normal daily activities as well as any action taken such as use of analgesic medication following the 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.

PIN Questionnaire (applicable to only Part 1 and Part 3)

Dimension score "acceptance of ISRs" and individual item score assessing pain will be evaluated by PIN Questionnaire. Refer to Section 10.9, Appendix 9 for PIN Questionnaire.

NRS Questionnaire

Post-injection/infusion pain assessment will be scored as specified in the SoA (Section 1.5, Section 1.6, and Section 1.7) by NRS from 0 to 10 (0: CCI [redacted], 10: CCI [redacted]). Refer to Section 10.8, Appendix 8 for NRS.

8.3. Pharmacokinetics

Whole blood samples of approximately 2 mL will be collected for measurement of concentrations of GSK3810109 and rHuPH20 as specified in the SoA (Section 1.5, Section 1.6, and Section 1.7).

- 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 PK of GSK3810109. Each blood sample will be processed into serum and divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of GSK3810109 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- PK Samples will be analyzed using an appropriately validated assay method by or under the supervision of the sponsor.
- For Part 3, CCI [redacted]

8.4. Genetics

Genetics are not evaluated in this study.

8.5. Immunogenicity Assessments

Antibodies to GSK3810109 will be evaluated in serum samples collected from all participants according to the SoA (Section 1.5, Section 1.6, and Section 1.7). 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.

Serum samples will be screened for antibodies binding to GSK3810109 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to GSK3810109 and/or further characterize the immunogenicity of GSK3810109.

The detection and characterization of antibodies to GSK3810109 will be performed using a validated assay method by or under the supervision of the sponsor. Samples collected for detection of antibodies to study intervention may also be evaluated for GSK3810109 serum concentration as described in Section 8.3 to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Samples may be stored according to local regulations following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to GSK3810109.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Analyses will be performed separately for each study part, and will be the same across study parts, unless otherwise stated.

There is no formal research hypothesis that will be statistically tested in this study.

9.1.1. Multiplicity Adjustment

There is no multiplicity adjustment required for this study.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Screened	All participants who will be screened for eligibility.
Enrolled	All participants who sign the ICF. Note that screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled Analysis Set as they did not enter the study.
Safety	All participants who receive at least 1 dose of study intervention.
PK Concentration	Participants who receive at least 1 dose of study intervention and have at least 1 assayed postdose sample of PK concentration data. This analysis population will be used in the assessment and characterization of PK concentrations.
PK Parameter	All participants in the PK population who received study intervention for whom valid and evaluable serum PK parameters are derived. This analysis population will be used in the assessment and characterization of PK parameters.

ICF = informed consent form; PK = pharmacokinetic(s)

9.3. Statistical Analyses

9.3.1. General Considerations

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section, as well as to provide details of any additional planned analyses. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

9.3.2. Primary Endpoints/Estimands Analysis

All safety analyses will be performed on the Safety Analysis Set.

The severity of AEs and SAEs will be determined by the investigator (Section 10.3). All reported AEs will be coded using MedDRA and summarized by system organ class and preferred term. Estimands are presented in Section 3.

The number and percentage of participants with treatment-emergent AEs, SAEs, study product-related AEs, deaths, and AEs leading to study product or study withdrawal through Week 24 will be provided. The number and percentage of participants with elevated Grade 2 to 4 ALT or elevated Grade 2 to 4 AST values will be provided. The number and percentage of participants with treatment-emergent AEs will also be summarized by severity (grade), including (for Part 1 and Part 3) a categorization for AEs Grade 2 or higher. For Part 1 and Part 3, the number and percentage of participants who have ISRs within 7 days following study treatment administration will be provided.

Categorical results will be summarized using frequency measures (number and percentage) and numerical results will be summarized using descriptive statistics (eg., mean, standard deviation, minimum. median, maximum).

Additional analyses may be performed to further characterize the primary endpoints and will be detailed in the SAP.

9.3.3. Secondary Endpoints/Estimands Analysis

9.3.3.1. Pharmacokinetic Analysis

Serum GSK3810109 concentration-time data will be analyzed by PPD, under the oversight of Clinical Pharmacology Modeling & Simulation department within GSK/ViiV, using non-compartmental methods with *Phoenix*® *WinNonlin*® Version 8.0 or higher. Statistical analysis will be performed by PPD, under the oversight of Biostatistics, GSK/ViiV. Calculations will be based on the actual sampling times recorded during the study. Estimands are presented in Section 3.

Based on the individual concentration-actual time data the following serum PK parameters for GSK3810109 will be estimated as data permit:

AUC(0-inf) – Area under the plasma concentration-time curve from time zero extrapolated to infinity

AUC(0-t) – Area under the plasma concentration-time curve from time zero to time of last observed quantifiable concentration

Cmax – Maximum observed concentration

Tmax – Time of maximum observed concentration

t1/2 – Apparent terminal phase half-life

Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) will be summarized.

Other PK parameters, e.g. clearance, volume of distribution at steady state, and volume of distribution may also be derived as appropriate.

Blood concentration-time data from different parts of the study may be analyzed using a population approach. A non-linear mixed effects model will be used to determine population PK parameters and identify relevant covariates (e.g., age, weight, or disease related covariates). The data from this study may be combined with the data from other studies for a population PK analysis, which will be reported separately.

Further details of the PK analysis will be provided in the SAP.

9.3.3.2. Safety Analysis

Estimands are presented in Section 3.

For Part 1 and Part 3 only:

Analyses related to the severity and acceptance of pain and ISRs will be performed on the Safety Analysis Set.

Dimension scores “acceptance of ISRs” and individual item scores assessing pain at Day 2 and Day 7 using the PIN questionnaire data will be summarized using descriptive statistics. Number and percentage of participants reporting they were bothered or affected by the pain and local reactions based on the PIN Questionnaire will be provided for Day 2 and Day 7. Number and percentage of participants reporting ISRs overall and by grade will be provided. The duration of the ISRs will be summarized overall and by grade. Additional analyses may be performed to further characterize the secondary endpoints related to the severity and acceptance of pain and ISRs, and will be detailed in the SAP.

For Parts 1, 2, and 3 separately:

Post injection/infusion pain assessment scores based on a NRS from 0 to 10 (0: CCI , 10: CCI) will be summarized by the study day using descriptive statistics and also as the number and percentage of participants for each pain assessment score.

Change from baseline over time in laboratory parameters, ECGs, and vital signs will be summarized with descriptive statistics. For ECG values, the frequency in different categories of maximum post-baseline QTcF values, including maximum change from baseline in QTcF, will be provided. Details about the categories of maximum post-baseline QTcF values and maximum change from baseline in QTcF will be included in the SAP.

The frequency of laboratory abnormality events along with the shift from baseline to the worst-case post-baseline value will be provided. Abnormal liver chemistry results will be determined using increases above the ULN. Change from baseline values will be summarized with descriptive statistics.

Categorical results will be summarized using frequency measures (number and percentage) and numerical results will be summarized using descriptive statistics (eg., mean, standard deviation, minimum. median, maximum). Further details of the safety analysis will be provided in the SAP.

Additional analyses may be performed to further characterize the secondary safety endpoints and will be detailed in the SAP.

9.3.4. Exploratory Endpoints/Estimands Analysis

CCI [redacted]

Anti-drug antibodies to GSK3810109 will be monitored in the study. Further details of the analysis will be provided in the SAP.

9.4. Interim Analysis

An interim analysis is planned after all participants receiving SC administration in Part 1 complete their Week 24 visit. At that timepoint, the data available for participants receiving IV administration will also be analyzed and included. This interim analysis is planned to enable a preliminary assessment of the safety and PK of this compound to be used for the planning of future studies.

Further details will be provided in the SAP.

9.5. Sample Size Determination

The number of participants in this study is based on clinical and practical considerations and not on a formal statistical power calculation. The total sample size of approximately 8 participants in each part is considered sufficient for the objectives of the study.

A sufficient number of participants will be enrolled to ensure approximately 8 participants complete each part of the study for a total of approximately 24 participants in the study.

Participants who withdraw prior to study completion may be replaced.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (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, including the risk and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.
- 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 GSK3810109 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3810109 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 that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An SRT for GSK3810109 reviews emerging and cumulative data for GSK3810109 on a monthly basis. For Part 1, safety review decisions and the status of the enrollment process will be shared with an SRT at regular intervals and discussed during the monthly SRT meetings.

For Part 2, a core SRT for Study 217901 study will review data for both sentinel and non-sentinel participants of the study. For Part 3, the core SRT will review data for the 2 participants in the first cohort before enrolling the next 6 participants. The core SRT is composed of safety lead, medical monitors, and project biostatistician.

The SRT will make recommendations to the VSLC regarding safety findings, including study pause, modification, and termination. The VSLC is chaired by the ViiV Chief Medical Officer and will have the final decision on study modifications, including termination. Details regarding the VSLC membership and function are included within the VSLC Charter.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV/GSK site or other mutually agreeable location.
- ViiV/GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, ViiV/GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- 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/GSK Policy.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). This includes accurate and timely transcription of the data recorded on the participant-completed ISR diary cards (applicable to Part 1 and Part 3 of the study) into the relevant section of the study

eCRF. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- 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/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 eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. 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, and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered on the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered onto the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator.
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or

suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 2 will be performed by the central laboratory/the local laboratory.

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

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

Table 2 Protocol-required Safety Laboratory Tests

Laboratory Assessments	**Parameters**		
Hematology	Platelet count Red Blood Cell count Hemoglobin Hematocrit	Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	White Blood Cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Blood Urea Nitrogen Creatinine Glucose (fasting) Potassium Sodium Chloride Calcium	Carbon dioxide AST ALT Alkaline phosphatase[2]	Total and direct bilirubin Albumin Total protein
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal on dipstick)		
Pregnancy testing	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)		
Other Screening Tests	• Test for SARS-CoV-2 • Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Urine drug screen (alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opiates		

Laboratory Assessments	Parameters
	[including heroin, codeine, and oxycodone]) • HIV-1 and -2 antigen/antibody immunoassay, Hepatitis B (HBsAg), anti-HBc, (aHBcT), anti-HBsAg, HBV DNA (as needed) and hepatitis C antibody[3]

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.5. All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to ViiV/GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. 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).

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

10.3.1. Definition of AE

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

Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

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

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT ≥3 × ULN AND total bilirubin ≥2 × ULN (>35% direct bilirubin) or international normalized ratio >1.5 must be reported as an SAE. • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers,

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-up of AEs and SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to ViiV/GSK in lieu of completion of the ViiV/GSK required form. • There may be instances when copies of medical records for certain cases are requested by ViiV/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 ViiV/GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. • Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

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

10.3.4. Reporting of SAE to ViiV/GSK

SAE Reporting to ViiV/GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken 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 ViiV/GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the 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 data collection tool 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: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Participants of Childbearing Potential (POCBPs)

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 POCBPs.

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

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

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). In the absence of 12 months of amenorrhea, confirmation with more than 1 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.

10.4.2. Contraception Guidance:

Participants of childbearing potential are eligible to participate if they agree to use a method of contraception consistently and correctly as described in Table 3.

Table 3 Highly Effective Contraceptive Methods

CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[2] 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[2]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[2]
• 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[2] 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[3]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[3]
  • 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[4]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[5]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[3]

1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
2. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
3. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable

contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

4. 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.
5. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while he is 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 ViiV/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 ViiV/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 ViiV/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 ViiV/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 ViiV/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.

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

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3 × ULN
If ALT ≥3 × ULN AND bilirubin[1,2] ≥2 × ULN (>35% direct bilirubin) or INR >1.5, report as an SAE.
See additional Actions and Follow-up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow-up Assessments</th></tr>
<tr><td>• Immediately pause study
• Report the event to ViiV/GSK within 24 hours
• Complete the liver event eCRF, 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, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT ≥3 × ULN AND bilirubin <2 × ULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within 24 to 72 hours
• Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferase values show downward trend
• Obtain blood sample for PK analysis, obtained within 48 hours of last dose[4]
• Serum creatine phosphokinase and lactate dehydrogenase
• Fractionate bilirubin, if total bilirubin ≥2 × ULN
• 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 eCRF
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.
• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRF.</td></tr>
</table>

1. Serum bilirubin fractionation should be performed if testing is available. 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 ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody, hepatitis B surface antigen, and hepatitis B core antibody; 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. Pharmacokinetic sample may not be required for participants known to be receiving placebo or non- ViiV/GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw in the eCRF. 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 Study Reference Manual.

10.6. Appendix 6: COVID-19 Pandemic and Clinical Study Continuity

The COVID-19 pandemic may impact the conduct of clinical studies. Significant logistical challenges may arise from quarantines, variable restrictions on site resources and operations, site closures, travel limitations and the inability of an individual participant to attend clinic visits, interruptions to the supply chain for the investigational product, or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including dispensation of the investigational product to the participant or adhering to protocol-mandated visits and laboratory/diagnostic testing.

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 study treatment for participants enrolled in this clinical study.

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 study database.

This appendix outlines the measures that are approved for implementation within this clinical study, to protect participant safety, welfare, and rights, and to ensure data integrity and the integrity of the clinical study, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local IRBs/IECs 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.

10.6.1. 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 authorized/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 AEs, from the participant through alternative means, e.g., by telephone contact.
- There may be cases where the current principal investigator of a site is indisposed for a period and may need to delegate parts of his or 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 principal investigator 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/IRB/IEC regulations.

10.6.2. 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 ICF 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/EC agreement and approval.

10.6.3. COVID-19 Vaccines

Any active study 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 study 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 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.

10.6.4. 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.

10.6.5. COVID-19 Specific Data Capture

10.6.5.1. Capturing COVID-19-Specific Protocol Deviations

Please refer to the Study Reference Manual for specific details on capturing protocol deviations as a result of COVID-19.

10.6.5.2. Capturing COVID-19 Specific Adverse Events and Serious Adverse Events

ViiV Healthcare/GSK is monitoring the evolving situation with respect to COVID-19 carefully and the impact this may have on ongoing or planned clinical studies. It is important for the study team to describe COVID-19-related AEs/SAEs and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analyses.

Please use the following guidance:

1. Adverse events 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. Serious AEs 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 World Health Organization 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; the most recent definitions should be consulted for each case When reporting both serious and non-serious AEs (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, reporting, and decisions around the impact to study drug continuation in the setting of clinically defined mild COVID-19 infection.
5. A new COVID-19 infection eCRF will be included to collect additional details about the reported COVID-19 AE or SAE data. It is important that the correct information is collected from each participant reporting a COVID-19 AE or SAE. Therefore, please use the eCRF templates to help you collect this information for all COVID-19-related AEs/SAEs.

World Health Organization 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 participant 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 participant with any acute respiratory illness AND having been in contact (see definition of "COVID-19 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 participant with severe acute respiratory illness (fever and at least 1 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.

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

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS, 2017) is a descriptive terminology that can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

The table will be used as posted at the link above with the following exemptions:

- Weight loss will be recorded as an AE only if it is considered deleterious to the participant's health.
- For severity grading of the solicited bruising parameter at the product administration site, the definitions based on size of the largest diameter and listed for the "Injection Site Erythema or Redness" will be used. The severity grade definition for "Bruising" provided under the Dermatologic Clinical Conditions will be used only for unsolicited adverse events involving bruising at other body locations.
- Creatinine changes will be graded on the basis of the upper limit of normal provided by the grading table and not change from baseline.
- Creatinine clearance changes will be graded according to mL/minute provided by the grading table and not change from baseline.
- Subclinical comprehensive metabolic panel results for sodium, potassium, chloride, bicarbonate, BUN, and glucose will not be considered an AE unless Grade 2 or greater.

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

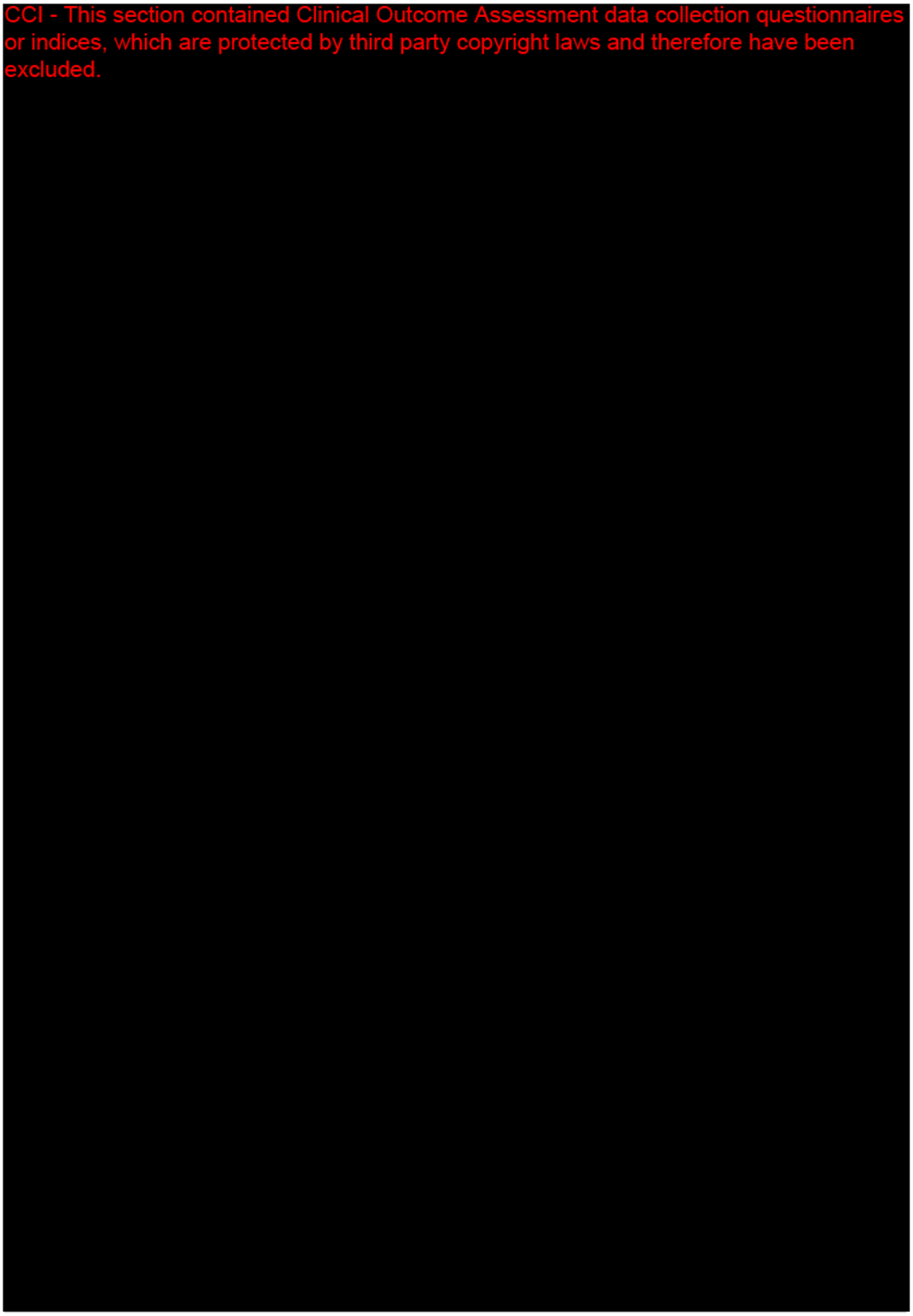
Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

10.8. Appendix 8: Numeric Rating Scale

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

10.9. Appendix 9: PIN Questionnaire (For Part 1 and Part 3 only)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.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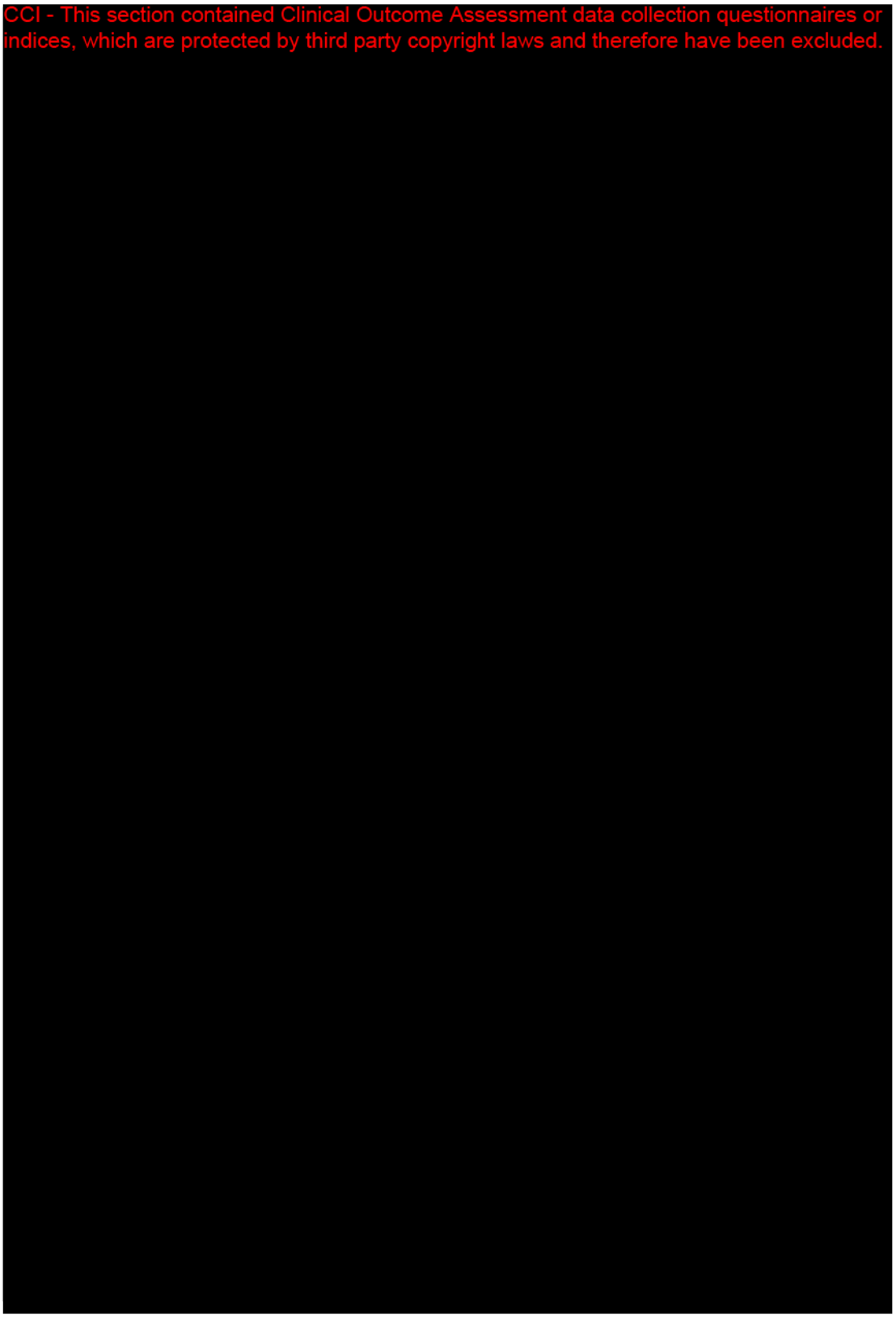
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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10.10. Appendix 10: Abbreviations and Trademarks

CCI	
AE	Adverse event
ADL	Activities of Daily Living
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-inf)	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time of last observed quantifiable concentration
bNAb	Broadly-neutralizing monoclonal antibody
CA	Competent Authority
CI	Confidence interval
CFR	Code of Federal Regulations
Cmax	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRS	Cytokine release syndrome
D	Day
DAIDS	Division of AIDS
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDP	ENHANZE™ Drug Product
EOI	End of Infusion
FcRn	Neonatal Fc-receptor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human
GCP	Good Clinical Practice
gp120	glycoprotein 120 subunit
GSK	GlaxoSmithKline
HA	Hyaluronan

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus-1
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous (ly)
LS	Leucine serine
MAb	Monoclonal antibody
NOAEL	no-observed-adverse-effect level
NIMP	Non-investigational medicinal product
NRS	Numeric rating scale
PIN	Perception of injection
PK	Pharmacokinetic(s)
POCBP	Participant of childbearing potential
PSRT	Protocol Safety Review Team
QD	Once daily
QTLs	Quality tolerance limits
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	Quality tolerance limit
rHuPH20	Recombinant human hyaluronidase PH20
SC	Subcutaneous (ly)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome-related coronavirus-2
SoA	Schedule of activities
SOI	Start of Infusion
SRT	Safety Review Team
t1/2	Apparent terminal phase half-life
Tmax	Time of maximum observed concentration

ULN	Upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
VSLC	ViiV Safety and Labelling Committee
VRC	Vaccine Research Center

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
DAIDS
Darzalex Faspro
EDP
Herceptin Hylecta
HyQvia/ HYQVIA
Mabthera
Phesgo
Phoenix
Rituxan
Rituxan Hycela
WinNonlin

10.11. Appendix 11: Protocol Amendment History

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

Amendment 01: 03-Jun-2022

Overall Rationale for the Amendment 01: The protocol is amended to include an additional dosing group (Part 2) which will include 8 new healthy participants who will receive a single 60 mg/kg dose of GSK3810109 administered intravenously.

Section # and Name	Description of Change	Brief Rationale
Throughout the document, as applicable	Sections were modified to accommodate IV administration of GSK3810109 designated as Part 2 of the study and language was updated to clarify procedures applicable only for SC administration, now designated as Part 1 of the study.	To clarify 8 new participants will be included in the study who will receive a single 60 mg/kg dose of GSK3810109 administered intravenously.
1.1 Synopsis and 10.1.5 Committees Structure	SRT composition was modified, and text was edited.	To reflect correct composition and to provide more clarity.
Section 5.2 Exclusion criteria	Following exclusion criterion was added: Positive test result for SARS-CoV-2.	This exclusion criterion was not previously included although a negative SARS-CoV-2 test was required prior to entry by the clinic.
Section 10.8 Appendix: Numeric Rating Scale	One of the NRS examples was removed.	The removed example of NRS was not being used in the study.
Throughout the document	Minor formatting and language changes were made.	For clarity and better readability.

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