Statistical Analysis Plan

Study ID: 217901

Official Title of Study: 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

NCT number: NCT05291520

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Information Type:	Statistical Analysis Plan (SAP)

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

Study Number: 217901

Compound Number: GSK3810109

Abbreviated 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

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND	148241

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TABLE OF CONTENTS

PAGE

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP 1.0	15Aug2022	217901/ Amendment 01 (06/03/2022)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe all planned interim and final analyses, including analyses to be included in CSR for study 217901.

Details and specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands, and Endpoints

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 (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	

Objectives	Endpoints
• To evaluate the PK of a single dose of GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants	• Assessment of 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-injection 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; NRS = Numeric Rating Scale; PIN = Perception of Injection; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; 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 in healthy adults?

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 condition: Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20. Part 2: Single 60 mg/kg IV dose of GSK3810109.
- Variables: Part 1: Incidence of adverse events (AEs; Grade 2 or higher) and serious adverse events (SAEs) through Week 24, incidence of injection site reactions (ISRs) within 7 days of GSK3810109 administration, and incidence of Grade 2 to 4 alanine aminotransferase (ALT)/ asparatate 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: Number and percentage of participants reporting AEs 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 (Parts 1 and 2):
    - Discontinuation from study for any reason: Treatment policy strategy (actual values of the variable will be used regardless of whether the intercurrent events has occurred) 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 Estimand: Interest lies in the safety and tolerability for a participant receiving a single SC dose of GSK3810109 co-administered with rHuPH20 or a single IV dose of GSK3810109.

Secondary estimand:

*Pharmacokinetic (PK) estimand***:**

A secondary question of interest is: What is the PK profile of a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20 in healthy adults or a single 60 mg/kg IV dose of GSK3810109 in healthy adults?

This secondary PK estimand is described by the following attributes:

- Population: Healthy male and female participants aged 18 to 65 years of age, inclusive.
- Treatment condition: Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20. Part 2: Single 60 mg/kg IV dose of GSK3810109
- Variables (Part 1 and Part 2):
    - Assessment of PK parameters: area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC(0-inf)), area under the plasma

concentration-time curve from time zero to time of last observed quantifiable concentration (AUC(0-t)), maximum observed concentration (Cmax), time of maximum observed concentration (Tmax), and apparent terminal phase half-life (t1/2)

- Summary measures (Part 1 and 2):
    - Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) will be summarized.
- Intercurrent events (Part 1 and Part 2):
    - 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).

Severity and Acceptance of Pain Estimand:

Other 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?

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 condition: 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.
- Variables:

Part 1:

- Dimension score and individual item score assessing pain at Day 2 and Day 7 from the perception of injection (PIN) Questionnaire.
- Following injection, prevalence 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.
- 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:

- 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 [redacted], 10: CCI [redacted]).
- 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-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 [redacted], 10: CCI [redacted]).

- Intercurrent events (Part 1 and Part 2):
  - Discontinuation from study for any reason: Treatment policy strategy (actual values of the variable will be used regardless of whether the intercurrent events has occurred) 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.

Safety estimand: Another 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?

These secondary safety estimands are described by the following attributes:

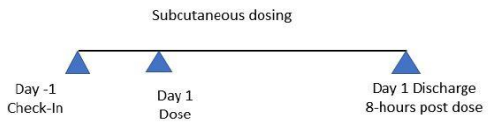
- Population: Healthy male and female participants aged 18 to 65 years of age, inclusive.
- Treatment condition: Part 1: Single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20. Part 2: Single 60 mg/kg IV dose of GSK3810109.
- Variables (Part 1 and Part 2): change from baseline in laboratory assessments, electrocardiograms (ECGs), and vital sign measurements.
- Summary measure (Part 1 and Part 2): Summary statistics for change from baseline in clinical laboratory assessments, ECGs and vital sign measurements.
- Intercurrent events (Part 1 and Part 2):
  - Discontinuation from study for any reason: Treatment policy strategy (actual values of the variable will be used regardless of whether the intercurrent event has occurred) 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.

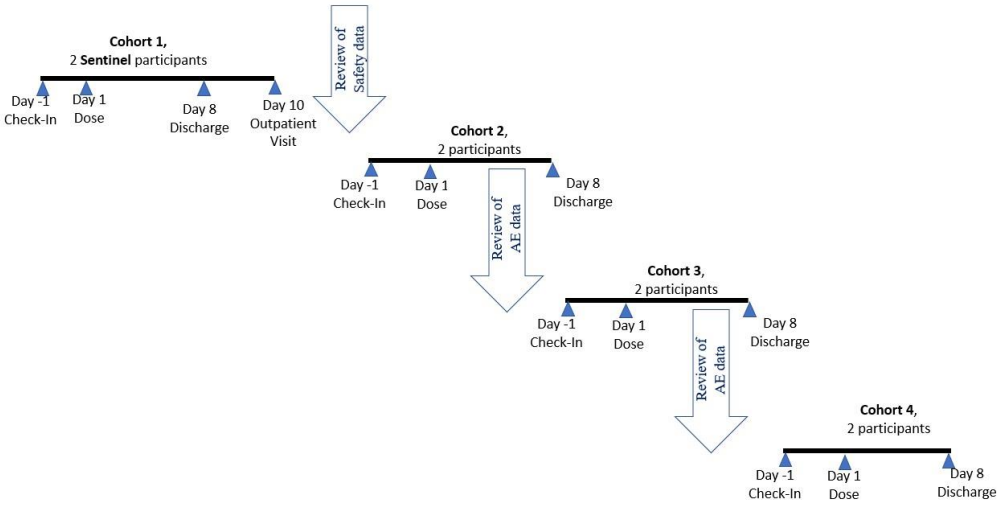
Exploratory estimand:

CCI

[redacted]

1.2. Study Design

Overview of Study Design and Key Features	
Design Features	• Phase 1, open-label, single dose study to assess safety, tolerability, and PK GSK3810109 administered SC with rHuPH20 or IV in healthy adult participants. The study comprises of 2 parts. • Part 1 includes approximately 8 participants who will receive a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20. • Part 2 includes approximately 8 participants who will receive a single 60 mg/kg IV dose of GSK3810109. Of these 8 participants, 2 participants will comprise a sentinel cohort. The other six participants will be included in 3 different cohorts of 2 participants each that will be dosed sequentially. • Study duration will be up to 24 weeks excluding screening. • In Part 1, participants will be admitted to the clinic on day -1 and will remain in the clinic for approximately 8 hours for study-related procedures after study product administration on day 1. In Part 2, participants will be admitted to the clinic on day -1 and will remain in the clinic for monitoring for 7 days after study product administration. <u>Study Schema:</u> Part 1  N= 8; All participants will receive a single 20 mg/Kg SC dose of GSK3810109, and be followed up for 24-weeks

Overview of Study Design and Key Features	
	Part 2  N= 8; All participants will receive a single 60 mg/Kg IV dose of GSK3810109, and be followed up for 24-weeks
Study intervention	Study interventions include GSK3810109 and rHuPH20. GSK3810109 is a sterile aqueous buffered solution filled into 10 mL single-dose vials. The drug dose in this study is 20 mg/kg body weight for SC infusion and 60 mg/kg body weight for IV infusion.
Study intervention Assignment	Study parts are sequential and therefore not randomized. All participants in part 1 of the study will receive a single 20 mg/kg SC dose of GSK3810109 co-administered with rHuPH20. All participants in part 2 will receive a single 60 mg/kg IV administration of GSK3810109.

2. STATISTICAL HYPOTHESES

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

2.1. Multiplicity Adjustment

There is no multiplicity adjustment requirement for this study.

3. ANALYSIS SETS

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

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who will be screened for eligibility.	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who sign the informed consent form (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.	• Study Population
Safety	• All participants who receive at least 1 dose of study intervention.	• Safety
Pharmacokinetic (PK) Concentration	• Participants who receive at least 1 dose of study intervention and have at least 1 assayed postdose sample of serum PK concentration data. • This analysis population will be used in the assessment and characterization of PK concentrations.	• PK
Pharmacokinetic 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.	• PK

4. STATISTICAL ANALYSES

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

4.1. General Considerations

Participants who withdraw prior to study completion may be replaced. Schedule of activities are outlined in protocol section 1.

The final planned analysis for parts 1 and 2 will be performed after the completion of the following steps in sequence:

1. All Part 1 participants have completed the study as defined in the protocol, database cleaning is performed, and database soft lock is achieved based on complete part 1 data and all available part 2 data at this stage.
2. Interim data analysis performed for preliminary assessment of safety and PK before final analysis is performed
3. All database cleaning activities have been completed and database hard lock has been declared by the data management

The term "Analysis Set" in the SAP will be referred to as "Population: in the displays; the term "Participant" in the SAP will be referred to as "Subject" in the displays of the OPS document.

Unscheduled visits will not be included in summary tables and/or figures but will be included in determination of worst-case on study intervention/post-baseline. All unscheduled visits will be included in listings.

4.1.1. General Methodology

Unless otherwise specified, continuous variables will be summarized using n, mean, median, standard deviation, minimum, and maximum in each category. Categorical data will be summarized as the number and percentage of participants in each category. All summaries will be presented by study part, where applicable.

4.1.2. Baseline Definition

Baseline is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of Endpoints

The primary endpoints for this study are:

Part 1:

- The number and percentage of participants who have AEs (Grade 2 or higher) and SAEs following GSK3810109 administration through week 24.
- The number and percentage of participants who have ISRs within 7 days following GSK3810109 administration.
- The number and percentage of participants who experience Grade 2 to 4 ALT/AST following GSK3810109 administration.

Part 2:

- 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 GSK3810809 IV administration through Week 24.

4.2.2. Main analytical approach

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

All reported AEs will be coded using MedDRA version 25.0 and summarized by system organ class (SOC) and preferred term (PT). Estimands are presented in Section 1.1.

The number and percentage of participants with treatment-emergent AEs, serious AEs, study product-related AEs, deaths, and AEs leading to study product or study withdrawal through Week 24 will be provided in a summary table. Treatment-emergent AEs are defined as any AEs that occur on or after the treatment start date and time. The summary table will also include the number and percentage of participants with treatment-emergent AEs summarized by severity (grade), including (for Part 1 only) a categorization for AEs Grade 2 or higher. If treatment relationship and severity of AEs are missing, no imputation will be performed. The number and percentage of participants who have Injection/Infusion site reactions within 7 days following study treatment administration will be provided.

Separate summary tables including all AEs, study product related AEs, SAEs and adverse events of special interest (AESIs) will be generated. These summary tables will be presented by SOC, PT, and maximum grade. Grade 2 or higher AEs and common AEs will be summarized by PT. Common AEs, defined as AEs occurring in more than 5% of participants in a study part, will be presented in descending order of total incidence by PT. In summary tables which are presented by SOC and PT, SOCs will be sorted in descending order of the total incidence then alphabetically; PTs will be sorted in descending order of the total incidence then alphabetically within the SOC. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity.

All AEs, AEs leading to withdrawal from the study, non-fatal SAEs, reasons for considering as a SAE, and death participant profile will be listed.

Additional details regarding AE definitions are presented in Section 4.5.2.

The number and percentage of participants who have ISRs within 7 days following study product administration will be provided for parts 1 and 2. Multiple symptoms of injection site reactions will be reported as separate AEs for each reported symptom. The number and percentage of participants who have ISRs will be summarized by preferred term and by the following classifications: 'Injection Site Abscess', 'Injection Site Anesthesia', 'Injection Site Bruising', 'Injection site cellulitis, 'Injection site discoloration', 'Injection site discomfort', 'Injection site erosion', 'Injection site erythema', 'Injection site hematoma', 'Injection site hemorrhage', 'Injection site itching', 'Injection site induration', 'Injection site nodule', 'Injection site pain', 'Injection site pressure', 'Injection site soreness', 'Injection site swelling', 'Injection site tenderness', 'Injection site warmth', and 'Other'. The incidence and duration of injection site reaction AEs overall and by grade, including the time at grade, will be summarized. All ISR AEs of a participant and the corresponding length of time of events will be considered for the summary table. If there are multiple events at each grade, the length of time would be equal to the average of all event times at a grade. Participants will be included in each grade level for which they had an event.

The ISR AEs will also be summarized by each preferred term for the following variables presenting the number and percentage of participants in each category: any grade and maximum grade (1, 2, 3, 4, and 5), maximum duration (1-7, 8-14, and >14 days), outcome, and number of

events (0, 1, 2, 3, 4, 5, 6-10, 11-15, 16-20, and >20 days). In addition, an event-level summary of injection/infusion site reaction AEs by preferred term will be created which includes the following information: any grade (1, 2, 3, 4, and 5), outcome, duration, and time to onset. Duration and time to onset will be analysed as continuous variables while number and percentage will be presented for the categories of other variables.

Injection Site Reactions (ISRs)
• ISRs will be presented by preferred term and according to the following classifications: o Injection site abscess o Injection site anesthesia o Injection site bruising o Injection site cellulitis o Injection site discoloration o Injection site discomfort o Injection site erosion o Injection site erythema o Injection site hematoma o Injection site hemorrhage o Injection site itching o Injection site induration o Injection site nodule o Injection site pain o Injection site pressure o Injection site soreness o Injection site swelling o Injection site tenderness o Injection site warmth o Other injection site reactions • Time to onset (day) of ISRs relative to injection will also be presented, where the time to onset (day) will be calculated as follows: ISR Start Date – Date of Injection + 1 • For ISR duration by grade (where grade is as specified by investigators in the eCRF), the interval between a change in grade will be assigned to the previous grade, or the grade at the start of the interval

The number and percentage of participants with Grade 2 to 4 ALT or Grade 2 to 4 AST values will be provided by study part.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Supportive secondary endpoint(s)

Definition of Secondary PK Endpoints:

The following serum PK parameters of GSK3810109 will be determined as data permit:

AUC(0-inf): Area under the serum concentration-time curve from time zero (pre-dose) extrapolated to infinite time; to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.

AUC(0-t): Area under the serum concentration-time curve from time zero (pre-dose) to the time of the last quantifiable concentration; to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.

Cmax: Maximum observed serum concentration determined directly from the concentration-time data.

Tmax: Time to reach maximum observed serum concentration

t1/2: Apparent terminal phase half-life (if possible)

Additional PK parameters may be calculated as data permit:

CL/F: Apparent total body clearance following extravascular administration

CL: Total body clearance following intravenous administration

Vz/F: Apparent volume of distribution following extravascular administration

Vss: Volume of distribution at steady state calculated for intravenous administration

PK Analyses:

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to GSK guideline VQD-GUI-000722 (6.0): Non-Compartmental Analysis of Pharmacokinetic Data and using the currently supported version of Phoenix WinNonlin (8.0 or higher) or using the currently supported version of SAS (9.4 or higher). All calculations of non-compartmental parameters will be based on actual sampling times.

Summary statistics (arithmetic mean, geometric mean, median, 95% CI [arithmetic and geometric], standard deviation [arithmetic and on ln-scale], minimum, maximum, and geometric between-participant CV (%CVb) for serum PK parameters will be summarized.

Serum concentration-time data will be listed for each participant and summary statistics will be calculated (i.e. arithmetic mean, 95% CI, standard deviation, CV%, median, minimum and maximum) by study part and planned sampling time. Individual serum concentrations will be plotted by treatment and nominal time on both linear and semi-logarithmic scales. Mean and median serum concentrations will be plotted by treatment and nominal time on both linear and semi-logarithmic scales.

The PK analyses will be based on (1) the PK Concentration Analysis Set for assessment and characterization of PK concentrations and (2) the PK Parameter Analysis Set for assessment and characterization of PK parameters.

Definition of Other Secondary Endpoints (Safety and Questionnaire Data):

Acceptance of ISRs and Individual Item Score Assessing Pain (Part 1 only): Acceptance of ISRs is assessed by the responses to Questions 17 and 18 of the PIN questionnaire. Dimension score is computed as the average of responses to Questions 17 and 18. Response to question 3 will be used to assess pain.

Bothered or Affected by Pain/Local Reactions (Part 1 only): Assessed based on the responses to each item in the PIN questionnaire and domain scores. The number and proportion of participants in each response category will be evaluated and domain scores will be summarized.

Post-Injection Pain Assessment: NRS responses will be used to assess pain after injection. The number and percentage of participants in each response level will be assessed.

Incidence and Duration of ISRs (Part 1 only): Number and proportion of patients who had ISRs will be evaluated. Duration of ISRs will be computed as the time between start and end of an ISR, inclusive of both start and end dates (end date-start date+1).

Change from baseline in Clinical laboratory assessments, ECGs, and vital sign measurements: The change from baseline will be assessed for each clinical laboratory, ECG, and vital sign assessments.

Other Secondary Endpoints Analyses:

All analyses for secondary safety and questionnaire data endpoints will be performed using the Safety Analysis Set. Estimands are presented in Section 1.1.

Questionnaire Assessments:

PIN questionnaire is only applicable for part 1 and is included in Section 6.1.5. Responses to the PIN questionnaire items at Day 2 and Day 7 will be summarized separately using descriptive statistics. Acceptance of ISRs dimension score is computed as the average of scores for questions 17 and 18 of the PIN questionnaire. Number and percentage of participants reporting they were bothered or affected by the pain and local reactions based on the responses to the items in the PIN Questionnaire will be provided for Day 2 and Day 7. Responses to each item in the PIN questionnaire will be summarized presenting the number and proportion of participants in each response category. Additionally, domain scores will be calculated using the information below:

Dimension Score (Chevat, 2008)

• Domains and Clusters
  ○ Bother from injection site reactions: items 3, 4, 5, 6, 7, and 8
  ○ Leg movement: items 11, 12, 15, and 16
  ○ Sleep: items 9, 10, 13, and 14
  ○ Acceptability: items 17 and 18
• 5 items not included in any of these domains and maintained as individual items (items 1, 2, 19, 20, and 21) (anxiety before, pain, satisfaction, anxiety after, and willingness)

- No overall score is calculated per the guidance in the Chevat, 2008 reference.
- The score of a domain is calculated as the mean of all non-missing items with the domain. Higher scores represent worse perception of injection
- A maximum of <50% items can be missing within a domain. Thus, if the number of missing items is ≥3 (Bother from injection site reactions), ≥2 (Leg movement/Sleep), ≥1 (Acceptability), then the total score for the domain should not be computed.

Individual Item Scores

- Items are rated on a 5-point scale, ranging from 1 CCI [redacted] to 5 CCI [redacted]
- Higher scores represent worse perception of injection.

Post-injection pain assessment scores based on a NRS from 0 to 10 (0: CCI [redacted], 10: CCI [redacted] will be summarized by the study day. NRS assessment scores will be reported by study part. The number and percentage of participants with each pain assessment score will be reported.

For part 1 only, number and percentage of participants reporting ISRs overall and by grade will be provided. The time to onset and duration of the ISRs will be summarized overall and by grade.

All data from PIN and NRS questionnaire assessments will be listed.

Laboratory Data:

Laboratory summaries will be presented by study part. Change from baseline in laboratory parameters will be summarized with descriptive statistics by timepoint. All laboratory data related to chemistry, hematology, and urinalysis will be listed separately for participants with any value outside of normal range. A listing will be produced including laboratory data with character results. Summary tables of maximum grade increase post-baseline relative to baseline will also be provided for hematology and clinical chemistry data. A summary table will be provided for worst-case urinalysis data relative to normal range post-baseline relative to baseline.

All liver monitoring/stopping events recorded on the CRF will be listed and summarized. Summary will be presented by study part. The number and percentage of participants with treatment-emergent liver monitoring/stopping events will be reported. Treatment-emergent events are any events that occur after the first dose of the

ECG:

ECG data summaries will be reported by study part. Change from baseline will be summarized by timepoint for ECG values. As triplicate measurements of ECG will be taken for all postdose timepoints, average of these assessments will be used for summary tables. For ECG values, the frequency in different categories of maximum post-baseline QTcF values, including maximum change from baseline in QTcF, will be provided. Categories for maximum post-baseline QTcF

values will include no change or decrease to ≤450 msec, increase to >450 to ≤480, increase to >480 to ≤500 msec, or increase to >500 msec and categories for maximum change from baseline in QTcF will include increase of ≤30 msec, increase of >30 to ≤60 msec, or increase of >60 msec. A separate summary table of ECG findings will be created. All ECG values and all ECG findings for participants with an abnormal finding will be listed separately. ECG values will include measurements of heart rate, PR, QRS, QT, and QTcF intervals.

Vital Signs:

Vital signs data summaries will be reported by study part. Vital sign assessments will include temperature, systolic and diastolic blood pressure, respiratory rate, and pulse. Change from baseline over time in vital signs and SPO2 will be summarized with descriptive statistics by timepoint. All vital signs data along with SP02 will be listed.

4.4. Exploratory Endpoint Analyses

CCI [redacted]

4.5. Safety Analyses

As safety endpoints for this study are primary and secondary endpoints, they are included in Section 4.2 and 4.3, respectively.

4.5.1. Extent of Exposure

The administered dose of GSK3810109 and rHuPH20 will be treated as continuous variables and summarized by study part. A listing of study drug exposure data will be produced.

4.5.2. Adverse Events

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.

The division of AIDS table for grading the severity of adult and pediatric adverse events (DAIDS, 2017), version 2.1, July 2017 will be used for AE reporting.

Further details on definitions of AEs and SAEs are included in protocol section 10.3. Analyses related to AEs are described in Section 4.2

4.5.2.1. COVID-19 Assessment and COVID-19 AEs

All COVID-19 assessments and symptoms will be listed. Separate summaries will be presented for COVID-19 assessments and symptoms. The summaries will be produced by study part. All COVID-19 related analyses will be based on the Safety Analysis Set.

4.6. Other Analyses

Past/ current medical conditions information recorded on the CRF will be presented in a listing and summarized. The summary will be produced by past/current medical conditions as well as the study part. This output will be based on the Safety Analysis Set.

4.7. Interim Analyses

An interim analysis is planned after all participants receiving SC administration in Part 1 complete the study. At that stage, all cleaned data available for participants receiving IV administration in Part 2 will also be included and analysed. The interim analysis is planned to enable a preliminary assessment of the safety and PK of this compound before final analysis is performed. The final analysis, on the other hand, will be performed after all database cleaning activities have been completed and final database lock has been declared by the data management.

All safety analyses mentioned in the SAP will be conducted as a part of interim analysis. PK analyses will use nominal sampling times and summary outputs from WinNonlin. As with the final analysis, no formal research hypothesis will be statistically tested in this study.

4.8. Changes to Protocol Defined Analyses

There were no changes to the originally planned statistical analyses specified in the protocol 217901/Amendment 01 dated 03-JUN-2022.

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.

Participants who withdraw prior to study completion may be replaced.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided by study part. Reasons for study withdrawal will be summarized. Study withdrawal reasons will be listed. Participant disposition summary will be based on the Safety Analysis Set. Study analysis sets will be summarized and participants excluded from any analysis set will be listed. Screening status and reasons for screen failure will be summarized based on the screened analysis set. Reasons for screen failure will also be listed based on the screened analysis set.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics, including age at screening, sex, ethnicity, race, height, weight, and body mass index (BMI) will be summarized with descriptive statistics. Age will be treated as a continuous variable. Demographic and baseline characteristics will be listed. Demographic and baseline characteristics summary and listing will be based on the Enrolled Analysis Set. The summary will be presented by study part. A listing of race will be produced based on the enrolled set.

6.1.3. Protocol Deviations

Important (significant) protocol deviations will be summarized. The summary will be presented by study part. All protocol deviations will be listed. All inclusion/exclusion criteria deviations will be listed. Protocol deviations and inclusion/exclusion criteria deviations analyses will be based on the Enrolled Set.

6.1.4. Concomitant Medications

Concomitant medications are defined as any medications and/ or vaccines received at the time of enrolment or during the study. All concomitant medications will be listed and summarized. Concomitant medications analyses will be based on the Safety Analysis Set.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Period

Screening: Screening is defined as the period between 21 days prior until 2 days prior (inclusive) to study drug administration

Check-in: Check-in is defined as the day before study drug administration

Intervention Period: Intervention period is defined as the day of study drug administration for part 1 and the time between day 1 and day 8 for part 2.

Follow-up: Follow-up is defined as the period between the day after until 167 days after (inclusive) study drug administration

6.2.2. Study Day

Study day is calculated as the number of days from the date of study drug administration (study product date).

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < First Study Product Administration Date → Study Day = Assessment Date – First Study Product Administration Date
- Assessment Date ≥ First Study Product Administration Date → Study Day = Assessment Date – First Study Product Administration Date + 1

6.2.3. Multiple measurements at One Analysis Time Point

Not applicable

6.2.4. Assessment/Visit Window

Assessment/visit windows will not be used for this study.

6.2.5. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • Where necessary, partial dates may be imputed for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of AEs), or elapsed time variables (e.g., time since diagnosis).

Element	Reporting Detail
Adverse Events/ Concomitant Medications/ Medical Conditions	• Imputations are used for sorting in data listings. • Partial dates for AE/ Concomitant Medications/ Medical Conditions recorded in the eCRF will be imputed using the following conventions: Missing start day o If study product administration date is missing (i.e. participant did not receive study product), then set start date = 1st of month. o Else if study product administration date is not missing: ▪ If month and year of start date=month and year of study product administration date then • If stop date contains a full date and stop date is earlier than study product administration date then set start date = 1st of month • Else set start date = study product administration date. ▪ Else set start date = 1st of month. Missing start day and month o If study product administration date is missing (i.e. participant did not receive study product), then set start date = January 1. o Else if study product administration date is not missing: ▪ If year of start date = year of study product administration date, then • If stop date contains a full date and stop date is earlier than study product administration date, then set start date = January 1. • Else set start date = study product administration date. ▪ Else set start date = January 1. Missing end day o A '28/29/30/31' will be used for the day (dependent on the month and year). Missing end day and month o A '31' will be used for the day and 'Dec' will be used for the month. Completely missing start/ end date o No imputation

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7. REFERENCES

1. Chevat, C., Viala-Danten, M., Dias-Barbosa, C., & Nguyen, V. H. (2009). Development and psychometric validation of a self-administered questionnaire assessing the acceptance of influenza vaccination: the Vaccinees' Perception of Injection (VAPI) questionnaire. Health and quality of life outcomes, 7, 21. https://doi.org/10.1186/1477-7525-7-21