Statistical Analysis Plan (SAP)

Study ID: 208021

Official Title of Study: An open-label, single dose study to investigate the pharmacokinetics, safety, tolerability, and immunogenicity of two dose levels of GSK3511294 administered subcutaneously in Chinese healthy participants

NCT ID: *NCT05140200*

Date of Document: 16-Jan-2023

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: An open-label, single dose study to investigate the pharmacokinetics, safety, tolerability and immunogenicity of two dose levels of GSK3511294 administered subcutaneously in Chinese healthy participants

Study Number: 208021

Compound Number: GSK3511294

Abbreviated Title: Phase 1 study of GSK3511294 in healthy Chinese participants

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clintrials.gov	NCT05140200

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	16 Jan 2023	27 Apr 2021	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 208021. Details of the planned interim analysis, as well as the final analyses, are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the 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 plasma pharmacokinetics of single subcutaneous doses of GSK3511294 in Chinese healthy participants	• Plasma pharmacokinetic parameters of GSK3511294 after a single subcutaneous dose: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vz/F, λz and t½ when assessable*
Secondary	
• To assess the safety and tolerability of single subcutaneous (SC) doses of GSK3511294 in Chinese healthy participants	• Incidence of adverse events (AE), serious adverse events (SAE) • Change from baseline in laboratory safety data, at each post-dose timepoint during the 26 week treatment period, which including hematology and clinical chemistry • Absolute values of C3 & C4 at each timepoint and the ratio to baseline at each post-dose timepoint during the 26 week treatment period • Change from baseline in vital signs, at each post-dose timepoint during the 26 week treatment period, which including blood pressure, body temperature and pulse rate

Objectives	Endpoints
• To assess the immunogenicity of GSK3511294 in Chinese healthy participants	• Change from baseline in Electrocardiograms (ECG), at each post-dose timepoint during the 26 week treatment period • Frequency and titres of binding anti-drug antibodies (ADAs) to GSK3511294, before and after GSK3511294 administration.

* PK parameter abbreviations: AUC(0-∞) = area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-t) = area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments; AUC(0-WeekN) = area under the concentration-time curve from time zero to WeekN; %AUCex = percentage of AUC(0-∞) obtained by extrapolation; Cmax = maximum observed concentration; tmax=time of occurrence of Cmax; tlast = time of last quantifiable concentration; CL/F = apparent clearance following subcutaneous dosing; Vz/F = apparent volume of distribution after subcutaneous administration; λz= terminal elimination rate constant; t½ = terminal phase half-life.

Primary Pharmacokinetic Estimand:

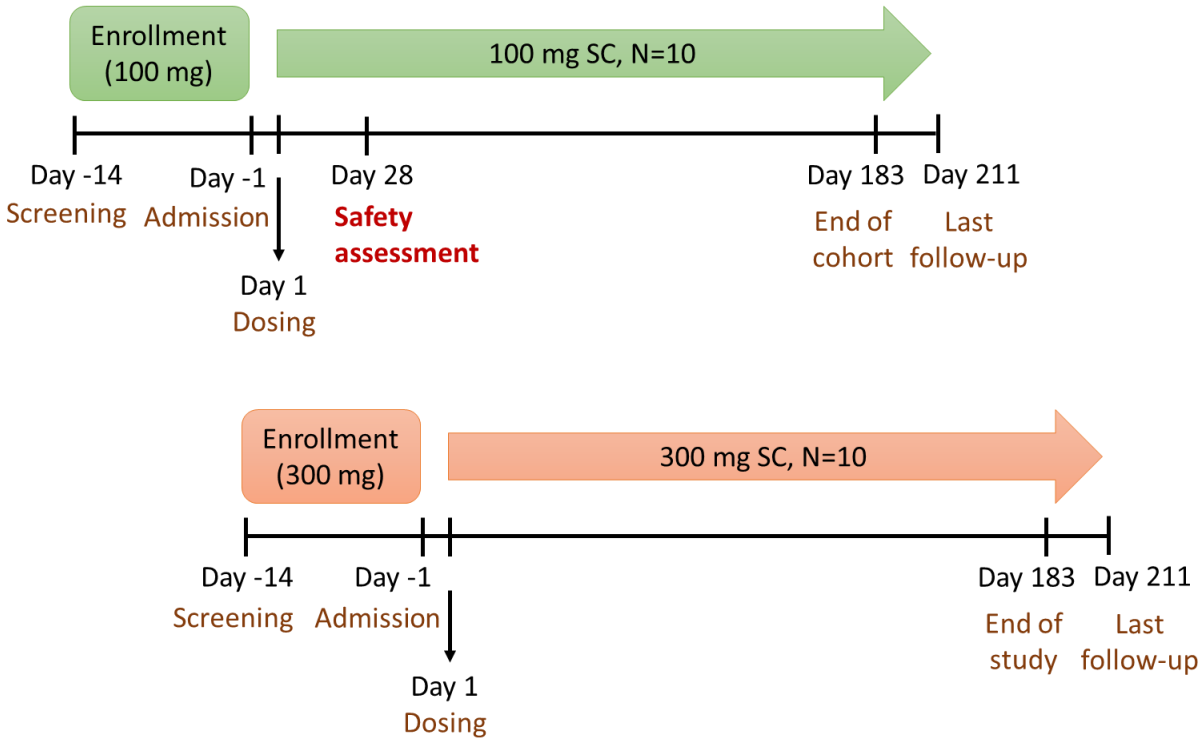
The primary clinical question of interest is: The pharmacokinetic target estimand aims to assess the PK profile in Chinese healthy participants with two dose levels of GSK3511294 administered subcutaneously in the absence of prohibited medication potentially impacting GSK3511294 PK profile.

The estimand is described by the following attributes:

Population	Chinese healthy male and female participants aged 18 to 45 years
Treatment	100 mg or 300 mg GSK3511294
Intercurrent events (ICE)	If use of prohibited medication is considered to impact on GSK3511294 PK profile, it will be addressed with hypothetical strategy and in such case the individual PK concentrations after ICE would be treated as missing in Non-compartmental analysis (NCA). Otherwise, it will be addressed with treatment policy and the individual PK concentrations after the occurrence of ICE will still be included into PK analysis.
Endpoints	Plasma pharmacokinetic parameters: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vz/F, λz and t½
Summary Measure	Geometric mean: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, CL/F, Vz/F, λz and t½ Median: tmax, tlast

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• This is a single-centre, single dose, open-label study to evaluate the pharmacokinetics, safety, tolerability and immunogenicity of subcutaneously administered GSK3511294 100 mg and 300 mg in Chinese healthy participants.
	• The study comprises 3 periods:
	  ○ Screening (2 weeks)
	  ○ Study period (26 weeks)
	  ○ Additional AE follow up period (4 weeks).

Study intervention	• Overview of Study Intervention

ARM Name	**GSK3511294**
Intervention Name	GSK3511294 Injection
Type	Biologic
Dose Formulation	Sterile liquid formulation in single use PFS
Unit Dose Strength(s)	100 mg/mL, 1.0 mL (deliverable)
Dosage Level(s)	100 or 300 mg (Day 1); 300 mg given as 3 separate injections given in the

<table>
<tr><th colspan="3">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td colspan="2"><table>
<tr><td></td><td>upper arm and separated by at least 5 cm.</td></tr>
<tr><td>Route of Administration</td><td>SC injection</td></tr>
<tr><td>Use</td><td>Experimental</td></tr>
<tr><td>IMP and NIMP</td><td>IMP</td></tr>
<tr><td>Sourcing</td><td>Provided centrally by the Sponsor</td></tr>
<tr><td>Packaging and Labelling</td><td>Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.</td></tr>
</table>
PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product
• There are no specific adjustment/stopping criteria for this study. Each participant will receive a single dose of GSK3511294 100mg or 300 mg subcutaneously in this study.</td></tr>
<tr><td>Study intervention Assignment</td><td colspan="2">• This is an open-label, single dose, non-randomized study.</td></tr>
<tr><td>Interim Analysis</td><td colspan="2">• No formal interim analysis is planned for this study.
• The 100mg cohort (10 participants) will be initiated first. The study team will review the safety data from the 10 participants in the 100mg cohort before initiating 300mg cohort: at least 4-week safety data. In case of safety concerns, further investigation of the safety concerns will be conducted (including reviewing PK data if deemed necessary) before initiating the 300 mg cohort. Criteria for Temporarily Delaying the start of the 300 mg cohort described in Section 5.5 of the Protocol.</td></tr>
</table>

2. STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate the pharmacokinetics of GSK3511294 100mg and 300mg administered subcutaneously. There are no formal hypothesis tests associated with this objective and no formal significance tests.

2.1. Multiplicity Adjustment

No multiplicity adjustment is planned.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	• Listings (unless specified otherwise)
Enrolled	All participants who entered the study (who received study intervention or underwent a post screening study procedure). Note 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 received at least one dose of study intervention. Participants will be analysed according to the intervention they actually received.	• Study Population • Safety
Pharmacokinetic (PK)	All participants in the Safety analysis set for whom at least one evaluable pharmacokinetic sample will be obtained and analysed. Participants will be analysed according to the intervention they actually received.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Safety analysis set will be used for all study population analyses and safety analyses, unless otherwise specified. The PK analysis set will be used for PK analyses. Study population and safety tables will be displayed overall and by dose level.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose of GSK3511294 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.

For ECG and/or Vital Signs analyses, if the latest, non-missing pre-dose values is from triplicate, the subject level baseline is defined as the mean of triplicate baseline assessments.

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

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic Population, unless otherwise specified.

4.2.1. Definition of Endpoint

4.2.1.1. Raw Plasma PK Concentrations

GSK3511294 plasma concentration-time data will be listed by dose level, study day, and nominal time.

4.2.1.2. Derived Plasma Pharmacokinetic Parameters

For each participant and for each dose, pharmacokinetic parameters described in Table 1 will be determined from GSK3511294 plasma concentration-time data, as data permit.

Table 1 Derived Pharmacokinetic Parameters

Parameter	Parameter Description

AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity will be calculated as: AUC(0-inf) = AUC(0-t) + C(t) / lambda_z
AUC(0-t)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-WeekX)	Area under the plasma concentration-time curve from zero to Week X will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Planned parameters are AUC(0-Week4), AUC(0-Week12) and AUC(0-Week26).
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: [AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100
Cmax	Maximum observed plasma concentration, determined directly from the plasma concentration-time data.
tmax	Time to reach Cmax, determined directly from the plasma concentration-time data.
tlast	Last time point where the concentration is above the limit of quantification.
CL/F	Apparent clearance CL/F=dose / AUC(0-inf)
Vz/F	Apparent volume of distribution.
λz	Terminal phase elimination rate constant. The number of points used to determine λz will also be reported.
t½	Apparent terminal phase half-life will be calculated as: t½ = ln2 / lambda_z

NOTES: Additional parameters may be included as required.

4.2.2. Main analytical approach

Plasma concentrations of GSK3511294 will be listed and summary statistics, including arithmetic mean, median, and standard deviations per GSK PK Display Standards, will be summarised by

dose and nominal time. Individual concentration-time profiles and median/mean profiles by GSK3511294 dose will be plotted on both linear and semi-logarithmic scale. Full details will be provided in the OPS.

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GSK. Plasma concentration-time data for GSK3511294 will be analysed by non-compartmental methods according to current working practices and using the currently supported version of WinNonlin version 8.0 (or higher). Calculations will be based on the actual sampling times recorded during the study.

All derived PK parameters will be listed. For each of these parameters, except Tmax and Tlast, the following summary statistics will be calculated for each dose level: median, minimum, maximum, arithmetic mean, 95% CI for the arithmetic mean, standard deviation, coefficient of variation (%CV = 100*(sqrt(exp(SD^2)-1))) (where SD = SD of natural log transformed data), geometric mean and 95% confidence interval for geometric mean. For Tmax and Tlast, median, minimum, maximum, arithmetic mean, 95% CI, and standard deviation will be calculated. The first point, last point and number of points used in the determination of λz will be included on the listing of the derived parameters.

4.3. Secondary Endpoints Analyses

The secondary endpoints analyses including safety analyses and immunogenicity analyses. The safety and immunogenicity analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.3.1. AEs and SAEs

4.3.1.1. Definition of endpoint(s)

The definitions of an AE or Serious Adverse Event (SAE) can be found in Appendix 3 of the

Protocol.

4.3.1.2. Adverse Event Analyses

Adverse events analyses including the analysis of AEs, SAEs, and other significant AEs will be based on GSK Core Data Standards. AEs will be coded using the standard MedDRA and grouped by system organ class.

A table will be provided with a high-level summary of the subject incidence of any AEs, on-treatment AEs, drug-related AEs, AEs leading to study withdrawal, any SAEs, on-treatment SAEs, drug-related SAEs, fatal SAEs and drug-related fatal SAEs.

Subject incidence of all on-treatment AEs, drug-related AEs, and AEs leading to study withdrawal will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of on-treatment AEs by system organ class, preferred term and maximum intensity.

Subject incidence and occurrence of common (≥ 5%) non-serious on-treatment AEs and serious on-treatment AE will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of non-serious drug-related AEs by preferred term in any dose cohort will be provided in descending order of frequency.

All AEs will be listed.

4.3.1.3. Adverse Events of Special Interest (AESI)

A summary table showing the number and percent of subjects, broken down by preferred term will be created using Hypersensitivity SMQ (narrow), Anaphylactic Reaction SMQ (narrow) and Vasculitis SMQ (narrow) as well as the number and percent of subjects with events of injection site reaction broken down by preferred term using MedDRA high level term (HLT) "Injection site reactions" under General disorders and administration site conditions SOC.

In addition, a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and whether it led to withdrawal from the study.

A listing will be produced for subjects reporting events under the specified above SMQs and MedDRA HLT.

4.3.1.4. COVID-19 Assessment and COVID-19 AEs

Number of participants with suspected, probable or confirmed for COVID-19 infection will be summarized according to the "COVID-19 Coronavirus Infection Diagnosis" and "COVID-19 Coronavirus Infection Assessment" eCRF page.

4.3.2. Laboratory Data

The hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Appendix 2 of the Protocol.

Change from baseline for Chemistry and Hematology will be summarized.

Change from baseline for laboratory values will also be summarized by visit and worst-case post-baseline using categories of "To Low", "To Normal or No Change" or "To High". The derivation rule follows:

- Laboratory values will be classified as "Low", "Normal", or "High" based on the provided normal ranges.
- Change from baseline values will be classified relative to normal range as "To Low", "To Normal or No Change", or "To High". Participants who do not change categories or move from out-of-range to normal will be classified as "To Normal or No Change".
- A "worst case post-baseline" change classification will be derived for each treatment in which participants will be counted in the "To Low" or "To High" categories if they reported a change from a "Normal" baseline to a value below or above the normal range, respectively, at any on-treatment scheduled, unscheduled, or early withdrawal visits.

Participants who did not report a change to a value outside the normal range at any visit will be counted in the "To Normal or No Change" category.

- Participants having both high and low values relative to normal ranges at post-baseline on-treatment visits for safety parameters will be counted in both the high and low categories of the "worst-case post-baseline" row of related summary tables.

Urinalysis results will be summarized.

The criteria for potential clinical importance refer to section 6.2.1.1.

4.3.3. Complement (C3 and C4)

Test results for Complement (C3 and C4) will be included within the laboratory data transfer and summarised by parameter and visit and presented as a table and as a figure. The summary table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, standard deviation (on log scale), median, minimum and maximum.

4.3.4. Vital Signs

Change from baseline for vital signs of Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Temperature, and Respiration Rate will be summarized.

Change from baseline for vital signs values of Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate will also be summarized by worst-case post-baseline using categories of "To Low", "To Normal or No Change", or "To High". The derivation rule is similar to Laboratory Data (section 4.3.2) except the classification is based on the following potential clinical importance specified in section 6.2.1.3.

4.3.5. ECG

A summary of the change from baseline in each ECG parameter by visit will be provided. When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

A summary of the number and percentage of subjects who had normal and abnormal ECG findings will be displayed by scheduled visits. When multiple ECGs were performed at the same planned timepoint, the worst-case finding will be summarized.

Change from baseline for ECG parameters will be summarized by worst-case post-baseline using categories of "To Low", "To Normal or No Change", or "To High". The derivation rule is similar to Laboratory Data (section 4.3.2) except the classification is based on the potential clinical importance specified in section 6.2.1.2.

The maximum post-baseline QTcF values will be summarized using the categories of:

- <450 msec
- 450 to 480 msec
- >480 to 500 msec

- >500 msec

The maximum post-baseline uncorrected QT interval values will be summarized using the categories of:

- ≤600 msec
- >600 msec

The maximum increase in post-baseline QTcF values relative to baseline will be summarized using the categories of:

- ≤30 msec
- >30 to 60 msec
- ≥60 msec

4.3.6. Immunogenicity Analyses

For the immunogenicity assessment, a binding antibody assay will be performed for anti-drug antibody (ADA).

The binding ADA results at each available timepoint, including Predose as well as at any time post-baseline, will be summarised. Summary statistics for the titre result will also be presented by visit.

The binding ADA results at each visit will be categorised as negative, transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). In addition, the highest post-baseline binding ADA confirmatory result obtained for a subject will be summarised. Subjects with both positive and negative results will be identified in the positive category. Summary statistics for highest titre result will also be presented.

A summary of adverse events by highest post-baseline binding ADA result will be produced.

A summary of positive confirmation binding ADA assay results in the subset of subjects who did not have a positive confirmation binding ADA result prior to the dosing of study treatment will also be presented.

4.4. Exploratory Endpoints Analyses

No exploratory endpoints analyses are planned as of now.

4.5. Safety Analyses

Please refer to section 4.3.

4.5.1. Extent of Exposure

This is an open-label, single dose study with two dose cohorts. Exposure data will be listed for the participants who received treatment.

4.6. Other Analyses

Population PK analyses may be conducted under the direction of CPMS. These analyses will be described in a separate document.

4.7. Interim Analyses

No interim analysis is planned in this study.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 27-April-2021).

5. SAMPLE SIZE DETERMINATION

There are no formal calculations of power or sample size for this study. The sample size of approximately 10 participants per cohort will be enrolled into the study to obtain at least 6 participants per cohort with at least 18-week PK data has been chosen based on feasibility.

Any impact of missing data and/or dropout will be assessed during the study. Specifically, in each cohort, if there are less than 6 participants with at least 18-week PK data, a maximum of up to 6 additional participants will be recruited in order to target at least 6 participants with at least 18-week PK data. In the case when there are less than 6 participants with at least 18-week PK data available in each cohort after the recruitment of additional participants, population PK analysis will be used to overcome the potential impact of missing data and/or dropout.

For each cohort, with 6 participants with at least 18-week PK data, assuming that the coefficients of variation% (CV%) of Cmax and AUC(0-∞) is 25.4% and 28.5% respectively (from global FTIH study, GSK Document Number 2019N411063_00), it is estimated that the lower and upper bounds of the 95% confidence interval (CI) would lie within 30.0% of the point estimate for Cmax and 34.1% of the point estimate for AUC(0-∞).

5.1. Sample Size Sensitivity

Different participant numbers with at least 18-week PK data and the corresponding precisions of Cmax and AUC(0-∞) are provided in the table 2 below. It assumes the CV% of Cmax and AUC(0-∞) is 25.4% and 28.5% respectively.

Table 1 Different Participant Numbers and Corresponding Precisions

Pharmacokinetic parameter	PPD	Precision (Half width of 95% confidence interval)
Cmax		30.0%
		26.0%
		23.2%
		21.2%
		19.6%
AUC (0-∞)		34.1%
		29.5%
		26.3%
		24.0%
		22.1%

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Safety Analysis Set. A summary of the number of participants in each of the participant level analysis set will be provided based on Screened Analysis Set.

Study population analyses including analyses of participant disposition, demographic and baseline characteristics, protocol deviations, and prior and concomitant medications. Details of the planned displays are presented in OPS document.

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. Reasons for study withdrawal and outcome of adverse events which led to study withdrawal will be summarized. Additionally, screening status and reasons for screen failure will be summarised.

Listings of reasons for screen failure and reasons for study withdrawal will be generated.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height, weight, body mass index (BMI) at screening and race will be summarized with descriptive statistics. In addition, the following age categories will be summarized: 18-64 based on the Safety Analysis Set. Body Mass Index (BMI) is calculated as weight (kg)/ [height (m)]^2, will be presented as for summary statistics with 1 decimal place.

A summary of family history of cardiovascular risk factors will be provided.

Past medical conditions and current medical conditions as of screening will be summarized respectively.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

No per-protocol analysis is planned for this study.

6.1.4. Prior and Concomitant Medications

Prior and concomitant medication tables will report by Anatomical Therapeutic Chemical (ATC) level 1 and ingredient. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classification of the ingredients.

Summaries will be provided for the medications by prior medications, pre-treatment concomitant medications, and on-treatment concomitant medications.

Study phase for concomitant medication

Study Phase	Definition
Prior	If concomitant medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not considered as prior. These will be further split into those that were started prior to dosing and those started after dosing as follows: • Pre-Treatment: Start Date and Time < Dosing Date and Time • On-Treatment: Start Date and Time >= Dosing Date and Time

6.1.5. Study Intervention Compliance

Not applicable.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

No additional analyses due to the COVID-19 pandemic are planned as of now.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

In addition, the following criteria will be used to flag potential clinical importance:

6.2.1.1. Laboratory Values

Haematology			
Parameter	**Units**	**Category**	**Clinical Concern Range**

			Low Flag (< x)	High Flag (> x)
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		130	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	15
%Reticulocyte	%		0.5	1.5

Clinical Chemistry				
Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (> x)**
Albumin	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	∪mol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Parameter	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

6.2.1.2. ECG

Parameter	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Absolute			
Absolute QTcF Interval	msec		> 450 [1]
Absolute PR Interval	msec	< 110 [1]	> 220 [1]
Absolute QRS Interval	msec	< 75 [1]	> 110 [1]
Absolute QT	msec		> 600
Change from Baseline			
Increase from Baseline QTcF	msec		> 60 [1]

NOTES: [1] Represent standard ECG Values of PCI for HV studies.

6.2.1.3. Vital Signs

Parameter	**Units**	**Clinical Concern Range**

		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

6.2.2. Study Phases and Treatment States

Assessments and events will be classified according to the time of occurrence relative to dosing.

6.2.2.1. Treatment States for Safety and Pharmacodynamic Data

Treatment State	Definition
Pre-Treatment	Date and Time ≤ Dosing Date and Time
On-Treatment	Date and Time > Dosing Date and Time

6.2.2.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If the medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not considered as prior. These will be further split into those that were started prior to dosing and those started after dosing as follows: • Pre-Treatment: Start Date < Dosing Date • On-Treatment: Start Date >= Dosing Date

NOTES: Please refer to section 6.2.6: Handling of Missing and Partial Dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

6.2.2.3. Study Phases for Adverse Events

Study Phase	Definition
Pre-Treatment	AE Start Date and time < Study Treatment Start Date and time
On-Treatment	If AE Start date and time ≥ Study treatment start date and time

Onset Time Since Dose (Days)	If Dose Date > AE Start Date = AE Start Date - Treatment Start Date If Dose Date ≤ AE Start Date = AE Start Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE End Date - AE Start Date + 1
Drug-related	If relationship is marked 'YES' on Inform/CRF OR value is missing.

6.2.2.4. Treatment Emergent Flags for Adverse Events

Flag	Definition
Treatment Emergent	• If AE start date is on or after treatment start date

NOTES: Time of study treatment dosing and start/stop time of AEs should be considered.

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

- Scheduled and unscheduled assessments will be considered for summary tables that display data by visit.
- All scheduled and unscheduled data will be considered for each assessment window.
- In summary tables, only scheduled timepoints for that cohort and assessment will be displayed. For example, complement data are not expected to be collected at all timepoints; if any complement data were taken e.g. at Week 2 then they will not be summarised.
- Only 1 value per participant, assessment and assessment window will be used in the calculation of summary statistics for that assessment; if a participant has more than 1 valid observation within an assessment window then the observation closest to the planned time will be used. If 2 observations are equidistant from the planned timepoint then the mean of the values will be taken.
-

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Safety and Complement (C3 & C4) data presented by visit.	ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day -1	Any time on Day -1. Note that if there is no scheduled Predose-assessment for the parameter then latest valid result prior to Day 1 dosing should be used		Day -1
	Immunogenicity, ECG, vital signs	Day 1 (Predose)	≤ 2h prior to dosing time		Day 1 (Predose)
	ECG, vital signs	Day 1 (2h)	Day 1 (1.25h)	Day 1 (2.75h)	Day 1 (2h)
	ECG, vital signs	Day 1 (8h)	Day 1 (7.25h)	Day 1 (8.75h)	Day 1 (8h)
	ECG, vital signs, haematology	Day 2 (24h)	Day 2 (23h)	Day 2 (25h)	Day 2 (24h)
	ECG, vital signs, haematology	Day 3 (48h)	Day 3 (47h)	Day 3 (49h)	Day 3 (48h)
	ECG, vital signs, haematology	Day 5	Assessment must have been done on Day 5		Day 5
	ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day 8 (Week 1)	± 1 day		Day 8 (Week 1)
	ECG, vital signs, heamatology	Day 15 (Week 2)	± 1 day		Day 15 (Week 2)
	Immunogenicity, ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day 29 (Week 4)	± 3 day		Day 29 (Week 4)
	ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day 57 (Week 8)	± 3 day		Day 57 (Week 8)
	Immunogenicity, ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day 85 (Week 12)	± 3 day		Day 85 (Week 12)

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
	ECG, vital signs, heamatology	Day 127 (Week 18)	± 3 day		Day 127 (Week 18)
	ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day 169 (Week 24)	± 3 day		Day 169 (Week 24)
	Immunogenicity, ECG, vital signs, laboratory (clinical chemistry, urinalysis and heamatology), complement (C3 & C4)	Day 183 (Week 26)	± 3 day		Day 183 (Week 26)

6.2.5. Multiple measurements at One Analysis Time Point

Mean of the measurements (e.g., ECG) will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.

If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken.

Participants having both High and Low values for Normal Ranges at any post-baseline visit (including post-baseline unscheduled assessments) for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

6.2.6. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day or Start Time: First day of the month or start of the day will be used, respectively, unless this is before the start date or time of study treatment; in this case the study treatment start date and time will be used and hence the event is considered On-treatment as per section 6.2.2: Study Phases and Treatment States.

Element	Reporting Detail
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is start date, a '01' will be used for the day and 'Jan' will be used for the month. o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
Age	• Only year of birth is collected on eCRF. Day and Month of birth are imputed as 30 June. Age is derived using the date of the screening visit. • All participants with imputed age of 17 or 18 years will be source data verified, and presence/ absence of protocol deviation on the inclusion criteria #1 will be taken into consideration in the derivation for the analysis variable age. • Birth date will be presented in listings as 'YYYY'.

6.2.7. Abbreviations & Trademarks

6.2.7.1. Abbreviations

Abbreviation	Description
ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments

Abbreviation	Description
AUC(0-Week x)	Area under the concentration-time curve from time zero to Week x
BMI	Body Mass Index
C	Complement
CI	Confidence Interval
CL/F	Apparent Clearance Following Subcutaneous Dosing
Cmax	Maximum Observed Concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
CV	Coefficient of Variation
DBF	Database Freeze
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FTIH	First Time in Humans
GSK	GlaxoSmithKline
HLT	High Level Term
ICE	Intercurrent Event
IMP	Investigational Medicinal Product
λz	Terminal phase elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of participants with available data
NCA	Non-compartmental Analysis
NONMEM	Non-linear Mixed-effects Modelling
OPS	Output and Programming Specification
PCI	Potential Clinical Importance

Abbreviation	Description
PFS	Pre-filled Safety Syringe
PK	Pharmacokinetic
QTcF	Fridericia's QT Interval Corrected for Heart Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
t½	Terminal Phase Half-life
tlast	Time of Last Quantifiable Concentration
tmax	Time of Occurrence of Cmax
Vz/F	Apparent Volume of Distribution.
WBC	While Blood Cell

6.2.7.2. Trademarks

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7. REFERENCES

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