Statistical Analysis Plan Amendment 3

Study ID: 214099

Official Title of Study: An Open-Label, Randomized, Single-Dose, Multicenter, Parallel-Group Study to Compare the Pharmacokinetics of Subcutaneous Depemokimab When Delivered with Safety Syringe Device or an Autoinjector in Healthy Adult Participants

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TITLE PAGE

Protocol Title: An Open-Label, Randomized, Single-Dose, Multicenter, Parallel-Group Study to Compare the Pharmacokinetics of Subcutaneous Depemokimab When Delivered with Safety Syringe Device or an Autoinjector in Healthy Adult Participants

Study Number: 214099

Compound Number: GSK3511294

Abbreviated Title: Phase I, Single-Dose Study to Compare the PK of Depemokimab When Delivered with a Safety Syringe Device (SSD)or an Autoinjector in Healthy Adult Participants.

Sponsor Name: GlaxoSmithKline Research & Development Limited

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP 1	28 October, 2022	Amendment 1, 16 March 2023	Not Applicable	Original version
SAP 2	27 March, 2023	Amendment 1, 16 March	Section 4.3.1.3- Main analytical approach-Summary statistics for C_{max} and AUC (0-∞), (arithmetic mean, geometric mean, median, 95% CI [arithmetic and geometric], standard deviation [arithmetic and on ln-scale], minimum, maximum, and geometric coefficient of variation [CV]) added.	Updated to include Primary PK parameters.
			Section-4.4 - Exploratory Endpoints- PK parameter (AUC(0-t), T_{max}, CL/F, Vz/F, λz, t1/2, Tlast and %AUCex) will be summarized at each nominal time point with descriptive statistics by injection site; by treatment group and injection site; by treatment group and baseline body weight category; by treatment group, injection site and baseline body weight category is added.	Updated in order to include AUC(0-t), T_{max}, CL/F, Vz/F, λz, t1/2, Tlast and %AUCex PK parameters
			Section-4.4- Exploratory Endpoints-GSK214099 plasma concentration-time data and derived PK parameters C_{max} and AUC(0-inf) along with (AUC(0-t), T_{max}, CL/F, Vz/F,	Updated in order to remove listings by all other combinations

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			λz, t1/2, Tlast and %AUCex) will be listed by injection site, study day, and nominal time.	of Treatment, Body Weight, Injection site.
			Section 6.1.2 - Demographic and Baseline Characteristics - Past medical conditions and current medical conditions as of screening will be summarized as "Summary of Past and Current Medical Conditions". In a single table.	Clarification
			Section 6.1.4-Prior and Concomitant Medications- Summaries will be provided only for the concomitant medications taken during treatment.	"Summary of Concomitant Medications Taken During Treatment" would be enough, since this is not critical to primary end point
			4.5.2. Adverse Event Analyses The frequency and percentage of AEs will be summarized in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT) only. Exposure adjusted incidence rate not required.	Exposure adjusted incidence rate not required as duration of study is short.
			4.5.2. Adverse Event Analyses Common (>=3%) AEs will be summarized by overall	Summarized by time to onset not required as

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			frequency. Summarized by time to onset removed.	duration of study is short.
			4.5.2. Adverse Event Analyses A separate summary will be provided for study intervention-related AEs. And SAE	Text updated for clarification
			4.5.3 Laboratory Data Summary of urinalysis removed. Summary of Worst-Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline added.	
			6.2.1.2 ECG ECG table updated.	
			4.1.1. General Methodology Plasma depemokimab concentration-time data will be analysed by PPD, under the oversight of the Clinical Pharmacology Modeling & Simulation department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher. Statistical analysis will be performed by Veramed, under the oversight of Biostatistics, GSK. Calculations will be based on the actual sampling times recorded during the study.	Text Added

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			4.5.6 ECG All ECG values for participants with protocol defined QT stopping criteria listing is removed.	
			4.6 Interim Analysis Interim analysis section updated to clarify that the 'Available PK concentration data from completed participants may be inspected to support development of depemokimab PK model. No changes to the conduct of the study will be implemented as a result of these analyses'	Clarification
			4.4 Exploratory Endpoint Analyses Analysis will be performed on the natural logarithms of AUC(0-t) using a fixed-effects analysis of covariance model	
SAP 3	15 Nov 2023	Amendment 1, 16 March 2023	4.5 Safety Analysis AESI of QTc prolongation will be summarized according to the ranges as detailed in Section 4.5.6	Section 4.5.6 is added.
			4.5.5 Vital signs The derivation rule is similar to Laboratory Data (Section 4.5.3)	Section reference was not right.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			4.5.5 Vital signs 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 relative to PCI ranges using categories of "To Low", "To Within Range or No Change", or "To High". Text is also modified in this section to make it clearer	Normal or No Change is changed to To Within Range or No Change since this output will be generated relative to PCI Criteria.
			6.2.6 Handling Partial dates Removed medical History from the list. Age is derived using the date of the screening visit.	We don't impute partial dates for medical History. Pre-screening visit was a typing error. We don't have it in study.
			4.5.3 Laboratory Data We will be summarizing Worst Case Results relative to PCI criteria Post Baseline relative to baseline. The derivation according to PCI Criteria is added in the section.	Initially we were only summarizing by the normal ranges.
			6.2.4 Assessment Window This section has been edited. Unscheduled/ withdrawal Visit Slotting Strategy Added.	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			4.1.1-General Methodology-Baseline Definition If for temperature and respiratory rate triplicate measurements are taken before dosing, then in those cases mean of the triplicate measurements will be taken.	
			4.5.6 ECG Change from baseline for ECG parameters will be summarized by worst-case post-baseline relative to PCI Criteria using categories of “To Low”, “To Within Range or No Change”, or “To High”.	
			6.2.2 Criteria for PCI-Haematocrit - Δ from BL removed from the list, Total CO2, Phosphorus also removed	
			4.8 Changes to Protocol Defined Analysis Text added regarding the possible exclusion of subjects from Primary PK Analysis.	This is due to the possible occurrence of SAE/PDs that can have substantial effect affect PK.
			4.3 Secondary Endpoint Analysis - PK Parameters will be Summarized and listed by injection site,	Initially Listing of PK parameters were not

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			study day, and nominal time.	included. This has been added.
			4.5.3 Laboratory Data- A scatter plot of Maximum post-baseline vs Baseline for ALT will be produced is added.	Added as per study team discussion
			4.2 Primary Endpoint Analysis- A table will also be produced for the primary ANCOVA analysis of Derived Plasma Depemokimab Pharmacokinetic Parameters { C_{max}, AUC(0-inf), AUC(0,t)} by Treatment to present the CV, R_Square/ Partial Eta-Square. The Estimates, Standard Error, Precision, of the estimates will also be presented.	Added as per study team discussion
			4.3.1.4 Immunogenicity Analysis- Plots for Adjusted Geometric Mean (95% CI) Ratio to Baseline Blood Eosinophils (10^9/L) by Visit will be produced. and Geometric Mean (95% CI) of Blood Eosinophils (10^9/L) by Visit will be produced. Scatter Plot of Individual Blood Eosinophil-Time Data by Highest Post-Baseline Binding Antibody Result will be produced.	Added as per study team discussion

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			4.4 Exploratory Endpoint Analysis- A table will also be produced for the exploratory ANCOVA analysis of Derived Plasma Depemokimab Pharmacokinetic Parameters { C_{max}, AUC(0-inf), AUC(0,t)} by Treatment to present the CV, R_Square/ Partial Eta-Square of the model. The Estimates, Standard Error, Precision of the estimates will also be presented.	Added as per study team discussion
			4.4 Exploratory Endpoint Analysis- Plots for Adjusted Geometric Means and Treatment Ratios (90% CI) for Primary Analysis of Derived Plasma Depemokimab PK Parameter C_{max}, AUC(0-inf), AUC(0,t) will also be produced	Added as per study team discussion
			4.4 Exploratory Endpoint Analysis- Plots for Individual Subject (+Geometric Mean and 95% CI) Derived Plasma Depemokimab PK Parameters C_{max}, AUC(0-inf), AUC(0,t) by treatment, by treatment and injection site, by Treatment and Baseline Body weight Category.	Added as per study team discussion
			4.1.1 General Methodology Summary statistics for PK concentration will include arithmetic mean, geometric	Added for clarification

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			mean, median, 95% CI [arithmetic], standard deviation [arithmetic and on ln-scale], minimum, maximum	
			4.5.2 Adverse Event Analysis Summary tables of AE and SAE will include both on-treatment and post-treatment data. That is AE and SAEs reported at any time post dose are summarized. Incidence, Relative Risk and Risk Difference SAE and AESI will be summarized.	Added

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 214099.

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 relative bioavailability of subcutaneous depemokimab following a single dose delivered with a safety syringe device (SSD)or an autoinjector in healthy adult participants	• C_{max} and AUC(0-inf) of depemokimab in plasma
Secondary	
• To assess additional PK parameters following a single dose of depemokimab delivered with a safety syringe device or an autoinjector in healthy adult participants	• AUC(0-t), T_{max}, CL/F, Vd/F, λz, T1/2, Tlast, and %AUCex of depemokimab in plasma
• To assess the immunogenicity of a single dose of depemokimab delivered with a safety syringe device or an autoinjector in healthy adult participants	• Incidence of immunogenicity as measured by the presence of antidrug antibodies and neutralizing antibodies to depemokimab
Safety	
• To assess the safety profile following a single dose of depemokimab delivered with a safety syringe device or an autoinjector in healthy adult participants	• Incidence of adverse events and serious adverse events • Change from baseline in laboratory parameters (including hematological and clinical chemistry parameters) and hepatobiliary laboratory abnormalities at discrete time points during the 26-week period • Change from baseline in vital signs (heart rate, systolic and diastolic blood pressure, body temperature) at discrete time points during the 26-week period • Change from baseline in electrocardiogram values at discrete time points during the 26-week period

Objectives	Endpoints
Exploratory	
• To evaluate depemokimab pharmacodynamic effects on blood eosinophil count following a single subcutaneous dose with a safety syringe device or an autoinjector in healthy adult participants	• Ratio to baseline in blood eosinophil count over time
• Device functionality	• User and device errors
• To compare the pharmacokinetics of subcutaneous depemokimab following a single dose administered in the upper arm, thigh, or abdomen	• Depemokimab measured concentration at planned visits, by anatomical site of injection • C_{max} and AUC(0-inf) of depemokimab in plasma, by anatomical site of injection

%AUCex = percentage of AUC(0-inf) due to extrapolation from Tlast to infinity; AUC(0-inf) = area under the concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the concentration-time curve from time zero to time of last observed quantifiable concentration; CL/F = apparent clearance following extravascular administration; C_{max} = maximum observed plasma concentration; λz = terminal elimination rate constant; T1/2 = terminal elimination half-life; Tlast = time of last measurable plasma concentrations; T_{max} = time to maximum observed plasma concentration; Vd/F = apparent volume of distribution following extravascular administration.

Primary Pharmacokinetic Estimand:

The primary question of interest is: to assess the relative bioavailability (assessed as ratio of the geometric mean of PK parameters maximum observed plasma concentration [C_{max}] and area under the concentration-time curve from time zero extrapolated to infinity [AUC(0-inf)]) of a single dose of depemokimab delivered with a SSD versus an autoinjector in healthy adult participants. The estimand is described by the following attributes:

Population	Healthy male and female participants 18 to 50 years of age inclusive
Treatment	Single subcutaneous dose of 100 mg depemokimab administered via a SSD versus via an autoinjector.
Intercurrent events (ICE)	Use of prohibited medication: Use of prohibited medication is not expected to impact the PK of depemokimab; therefore, treatment policy strategy will be used and the individual PK concentrations after the occurrence of the intercurrent event will still be included into PK analysis. • Handling of missing data: o For participants that withdraw prior to Week 18, or no PK concentrations are available until Week 18, it is anticipated that it will not be possible to derive the PK parameter AUC(0-inf). The participant will be excluded

	from the analyses related to AUC(0-inf) and no missing data imputation will be performed. For participants that withdraw prior to Week 4, or no PK concentrations are available until Week 4, it is anticipated that it will not be possible to derive a reliable value for the PK parameter C_{max}. The participant will be excluded from the analyses related to C_{max} and no missing data imputation will be performed. Rationale for Estimand: Use of prohibited medications is not expected to impact the PK of depemokimab.
Endpoints	Plasma pharmacokinetic parameters: C_{max} and AUC(0-∞)
Summary Measure	Ratio of the geometric mean of AI versus SSD for C_{max} and AUC(0-inf).

1.2. Study Design

Overview of Study Design and Key Features	
SSD= Safety Syringe Device	
Design Features	This is a Phase 1, randomized, multicenter, open-label, parallel-group, single-dose study in healthy adult participants. A single subcutaneous dose of depemokimab will be administered via a SSD or an autoinjector. The study will consist of a screening period, one treatment period, and a follow-up period. Participants will be screened within 30 days before the first dose of study intervention. Each participant will receive a single subcutaneous dose of depemokimab on Day 1 and will then be observed. Participants may be discharged from the clinic after all study procedures have been completed on Day 3. Participants will return for outpatient visits and receive a follow-up telephone call approximately 211 days after study intervention administration. Pharmacokinetic blood samples for the analysis of depemokimab will be collected prior to dosing on Day 1 and up to Day 183 after dosing. Including screening and the follow-up period, the total duration of the study is approximately 241 days.
Study intervention	Treatment A: a single subcutaneous dose of 100 mg depemokimab administered via a SSD Treatment B: a single subcutaneous dose of 100 mg depemokimab administered via an autoinjector
Study intervention Assignment	Participants will be randomly assigned in a 1:1 ratio to receive 1 of 2 treatments during the treatment period

Overview of Study Design and Key Features	
	The randomization will be stratified by body weight (<70 kg, 70 to <80 kg, and ≥80 kg). The site of injection will be randomized in a 1:1:1 ratio to the upper arm, abdomen, or thigh. All treatments will be administered by authorized study site staff.
Interim Analysis	No formal interim analysis is planned for this study.

2. STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate the relative bioavailability of subcutaneous depemokimab following a single dose delivered with a safety syringe device or an autoinjector in healthy adult participants. 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 device.

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the CRF.

Confidence intervals will use 90% confidence levels unless otherwise specified.

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

Blood sampling time will be related to the start of dosing. Linear and semi-logarithmic individual plasma concentration-time profiles (by treatment and by subject) and mean

(±SD) and median profiles will be plotted for each treatment. Plasma concentrations of depemokimab will be listed and summarised by treatment group and nominal time.

Summary statistics for PK concentration will include arithmetic mean, geometric mean, median, 95% CI [arithmetic], standard deviation [arithmetic and on ln-scale], minimum, maximum.

Summaries, including mean (±SD) and median profile plots, will also be produced by treatment group and injection site; treatment group and baseline body weight category (<70kg, 70-<80kg and ≥80kg); and treatment group, injection site and baseline body weight category. Any subjects randomised in error to the incorrect weight strata will be summarised based on the actual stratum per data collected in the CRF. Summaries of subjects by centre and treatment; centre, treatment, site of injection will be provided.

Baseline Definition

For all endpoints the baseline value will be 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.

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.

> Blood pressure and pulse will be measured in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements will be measured at all time points. If for temperature and respiratory rate triplicate measurements are taken before dosing, then in those cases mean of the triplicate measurements will be taken.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Plasma depemokimab concentration-time data will be analysis

Plasma depemokimab concentration-time data will be analysed by PPD, under the oversight of the Clinical Pharmacology Modeling & Simulation department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher. Statistical analysis will be performed by Veramed, under the oversight of Biostatistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of [endpoint(s)/estimands]

The pharmacokinetics of subcutaneous depemokimab following a single dose delivered with a safety syringe device vs an autoinjector will be analyzed by using AUC (0-∞), C_{max} 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
C_{max}	Maximum observed plasma concentration, determined directly from the plasma concentration-time data.

4.2.2. Main analytical approach

The analysis for the primary PK endpoints will be performed for the PK Population.

Pharmacokinetic analysis will be performed to compare the relative bioavailability of a single subcutaneous dose of 100 mg depemokimab administered via an autoinjector compared to a single subcutaneous dose of 100 mg depemokimab administered via SSD.

Based on the individual concentration-time data the following primary plasma PK parameters will be estimated:

C_{max} and AUC (0-∞) and AUC(0,t)

Analysis will be performed on the natural logarithms of AUC(0-inf) and C_{max} using a fixed-effects analysis of covariance model, with treatment and injection site as categorical covariates, and baseline weight as a continuous covariate fitted on the log scale. Effects will be estimated, and 90% CIs will be constructed for the following treatment comparisons:

Treatment B (Autoinjector) versus Treatment A (SSD)

Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.

A table will also be produced for the primary ANCOVA analysis of Derived Plasma Depemokimab Pharmacokinetic Parameters { C_{max}, AUC(0-inf), AUC(0,t)} by Treatment

to present the CV, R-Square/ Partial Eta-Square, of the model. The Estimates, Standard Error, Precision, of the estimates will also be presented.

4.3. Secondary Endpoint(s) Analyses

4.3.1. [Key/Confirmatory] secondary endpoint(s)

4.3.1.1. Definition of [endpoint(s)/estimands]

GSK214099 plasma concentration-time data and PK Parameters will be Summarized and listed by injection site, study day, and nominal time.

Immunogenicity assessment will be done for depemokimab delivered with a safety syringe device SSD or an autoinjector in healthy adult participants.

4.3.1.2. Derived Plasma Pharmacokinetic Parameters

For each participant pharmacokinetic parameters described in Table below will be determined from GSK214099 plasma concentration-time data, as data permit.

Parameter	Parameter Description
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-Week18). 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
t_{max}	Time to reach C_{max}, 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)

Parameter	Parameter Description
Vz/F	Apparent volume of distribution following extravascular administration.
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

4.3.1.3. Main analytical approach

The analysis for the secondary PK endpoints will be performed for the PK Population.

Summary statistics for C_{max} and AUC (0-∞), AUC(0-t), T_{max}, CL/F, Vz/F, λz, t1/2, Tlast and %AUCex (arithmetic mean, geometric mean, median, 95% CI [arithmetic and geometric], standard deviation [arithmetic and on ln-scale], minimum, maximum, and geometric coefficient of variation [CV]). For T_{max} and Tlast, median, minimum, and maximum only will be reported for each treatment group.

4.3.1.4. Immunogenicity Analyses

The immunogenicity assessment for anti-depemokimab antibodies will utilize a tiered analysis approach: an anti-drug antibody (ADA) binding assay that includes a screening assay, a confirmation assay and a titration assay; and a neutralizing antibody assay (NAb). The binding ADA and NAb results at each available timepoint, including Pre-dose as well as at any time post-baseline, will be summarised. Summary statistics for the titre result will also be presented by visit and treatment.

The binding ADA results at each visit will be categorised as a negative or positive, with sub-categories for 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), and available titre values. If a sample confirms positive, that participants is positive for ADA. Once a sample is characterized as negative, there will be no additional results for that sample. 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 titer result will also be presented (including min, median and max).

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.

A summary of neutralizing antibody assay results will summarise the neutralizing antibody assay results for participants with a positive binding antibody confirmatory assay result. Neutralising antibody assay results will be categorised as positive or negative. It will also summarise the highest postbaseline neutralizing antibody assay result obtained.

Immunogenicity Analysis- Adjusted Geometric Mean (95% CI) Ratio to Baseline Blood Eosinophils (10^9/L) by Visit and Geometric Mean (95% CI) of Blood Eosinophils (10^9/L) by Visit will be produced.

Scatter Plot of Individual Blood Eosinophil-Time Data by Highest Post-Baseline Binding Antibody Result will be produced.

Immunogenicity data will be listed for participants with at least one positive screening binding assay result.

4.4. Exploratory Endpoint(s) Analyses

To assess the pharmacodynamics of a single subcutaneous dose of depemokimab delivered with a safety syringe device or an autoinjector in healthy adult participants, the ratio to baseline of the eosinophil count will be summarized by treatment group with descriptive statistics. In addition, the absolute blood eosinophil count will be summarized by treatment group with descriptive statistics. Blood sampling time will be related to the start of dosing. Linear and semi-logarithmic individual plasma concentration-time profiles and mean (±SD) and median profiles will be plotted for each treatment.

To assess the pharmacokinetics of a single subcutaneous dose of depemokimab delivered in the upper arm, abdomen, or thigh in healthy adult participants, the measured depemokimab plasma concentration at planned visits and the derived PK parameters C_{max} and AUC(0-inf) along with (AUC(0-t), T_{max}, CL/F, Vz/F, λz, t1/2, Tlast and %AUCex) will be summarized at each nominal time point with descriptive statistics

- by injection site.
- by treatment.
- by treatment group and injection site.
- by treatment group and baseline body weight category.

- by treatment group, injection site and baseline body weight category.

GSK214099 plasma concentration-time data and derived PK parameters C_{max} and AUC(0-inf) along with (AUC(0-t), T_{max}, CL/F, Vz/F, λz, t1/2, Tlast and %AUCex) will be listed by injection site, study day, and nominal time.

Summaries, including mean (±SD) and median profile plots, will also be produced by treatment group, injection site, treatment group and injection site, treatment group and baseline body weight category (<70kg, 70-<80kg and ≥80kg), and treatment group, injection site and baseline body weight category. Any subjects randomised in error to the incorrect weight strata will be summarised according to the stratum corresponding to their actual treatment.

Additionally, a fixed-effects analysis of covariance model, with treatment and injection site as categorical covariates, and baseline weight as a continuous covariate fitted on the log scale and including an interaction term between treatment and injection site will be performed for the following PK endpoints:

C_{max}, AUC(0-inf) and AUC(0-t).

A table will also be produced for the exploratory ANCOVA analysis of Derived Plasma Depemokimab Pharmacokinetic Parameters { C_{max}, AUC(0-inf), AUC(0,t)} by Treatment to present the CV, R_Square/ Partial Eta-Square, of the model. The Estimates, Standard Error, Precision, of the estimates will also be presented.

Plots for Individual Subject (+Geometric Mean and 95% CI) Derived Plasma Depemokimab PK Parameters C_{max}, AUC(0-inf), AUC(0,t) by treatment, by treatment and injection site, by Treatment and Baseline Body weight Category.

Plots for Adjusted Geometric Means and Treatment Ratios (90% CI) for Primary Analysis of Derived Plasma Depemokimab PK Parameter C_{max}, AUC(0-inf), AUC(0,t) will also be produced.

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Definition of endpoint(s)

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

4.5.2. Adverse Event Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

Summary tables of AE and SAE will include both on-treatment and post-treatment data. That is AE and SAEs reported at any time post dose are summarized.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

The frequency and percentage of AEs will be summarized in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT) 2) in descending order by SOC, PT and Maximum Intensity.

Common (>=3%) AEs will be summarized by overall frequency.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. The summary Table will be displayed in descending order by SOC and PT.

A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary Table will include events with the relationship to study intervention as ‘Yes’ or missing

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary Tables will be displayed in descending order by SOC and PT.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as “Yes”. The summary Table will be displayed in descending order by SOC and PT.

Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK3511294 program include:

• Allergic reactions including anaphylaxis

Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis.

• Type III hypersensitivity (immune complex disease/vasculitis) reactions

• Local injection site reactions

• QTc prolongation

Summary tables of AESI will include both on-treatment and post-treatment data. That is AESIs reported at any time post dose are summarized.

AESI reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Vasculitis events and local injection site reactions are also collected via targeted eCRF within the study.

Separate summary Tables showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created.

For each type of AESI (excluding QTc prolongation) 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 action taken.

Incidence, Relative Risk and Risk Difference SAE and AESI will be summarized.

AESI of QTc prolongation will be summarised as detailed in Section 4.5.6 ECG.

Adverse event data will also be summarised by ADA assay category result.

4.5.3. Laboratory Data

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

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

Change from baseline for Chemistry and Haematology will be summarized.

Change from baseline for laboratory values will be summarized by visit.

Summary of worst-case laboratory results relative to PCI Criteria post-baseline relative to baseline will be done using categories of “To Low”, “To Within Range or No Change” or “To High”.

Summary of worst-case laboratory results relative to normal ranges post-baseline relative to baseline will be done 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.

  Laboratory values will be classified as “Low”, “Within Range”, or “High” based on the provided PCI 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”.

  Change from baseline values will be classified relative to PCI ranges as “To Low”, “To Within Range 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 Within Range or No Change”.

- A “worst case post-baseline” change classification relative to normal ranges 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.

  A “worst case post-baseline” change classification relative to PCI Ranges 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 “Within Range” baseline to a value below or above the within range, respectively, at any on-treatment scheduled, unscheduled, or early withdrawal visits. Participants who did not report a change to a value outside the within range at any visit will be counted in the “To Within Range 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.

Participants having both high and low values relative to PCI 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

A scatter plot of Maximum post-baseline vs Baseline for ALT and maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver

monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody are collected at baseline visit and if clinically indicated post baseline, analysed on as needed basis and will be summarised only for participants with data available.

The details of the planned displays will be in OPS.

Hepatobiliary Laboratory Abnormalities will be summarized. Summary of Worst-Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline will be summarised.

4.5.4. 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.

4.5.5. 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 relative to PCI ranges using categories of “To Low”, “To Within Range or No Change”, or “To High”. The derivation rule is similar to those mentioned for PCI criteria of Laboratory Data (Section 4.5.3)and the classification (PCI ranges) is based on the following potential clinical importance specified in Section 6.2.1.3.

4.5.6. 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 baseline assessments.

A summary of the number and percentage of subjects who had normal and abnormal ECG findings will be displayed by scheduled visits. Abnormal will include sub-categories of Clinically significant and non-clinically significant according to eCRF classification. When multiple ECGs were performed at the same planned timepoint, the worst-case finding will be summarized, except at baseline mean of triplicate baseline assessments will be taken.

If multiple meet criteria of worst case, then take the earliest.

Change from baseline for ECG parameters will be summarized by worst-case post-baseline relative to PCI Criteria using categories of “To Low”, “To Within Range or No Change”, or “To High”. The derivation rule is similar to those of PCI criteria of the Laboratory Data (Section 4.5.3) and the classification(PCI ranges)is based on the potential clinical importance specified in Section 6.2.1.2

Individual maximum QTcF values will also be summarised to show the number of subjects with maximum values (msec) that increased to the following categories: Decrease, no change or increase to <= 450, increase to 450 < to <= 480, increase to 480 < to <= 500, increase to 500< to <=530 and increase to > 530. QT uncorrected values will be summarised to show the number of subjects with maximum values in the following categories: <600 and >=600.

Additionally, individual maximum changes from baseline in QTcF values will be summarised to show the number of subjects with maximum changes (msec) in the categories: increase of <= 30, increase of 31 to 60 and increase of > 60.

4.6. Other Analyses

No subgroup analysis is planned in this study

4.7. Interim Analyses

No formal interim analysis is planned; however, if recruitment is significantly slower than anticipated, then a single interim analysis may be conducted to assess variability, and which could result in a re-estimation of the sample size. Available PK concentration data from completed participants may be inspected to support development of depemokimab PK model. Model development details will be reported outside the CSR. No changes to the conduct of the study will be implemented because of these analyses

4.8. Changes to Protocol Defined Analyses

The study team will review PDs and SAEs to see if they have an impact on PK prior to data analysis.

If a PD or SAE is found in any subject during data review which has the potential to significantly impact the PK, then it will be decided whether we should exclude such subjects from the primary PK analysis. If the decision is to exclude, then the subject number of the subjects along with the reason of exclusion will me mentioned in the footnote of the output of the primary PK analysis

A sensitivity analysis for the primary endpoint may be conducted to evaluate the impact of subject exclusions.

5. SAMPLE SIZE DETERMINATION

A total of approximately 126 (63 per treatment group) participants will be required to complete at least Week 18 of the study.

The primary aim of this study is to estimate the relative bioavailability of the autoinjector compared with the PFS. Therefore, the sample size calculation for this study is based on the number of participants needed to achieve an acceptable level of precision in the estimate of relative bioavailability.

The variability of depemokimab PK parameters (AUC and C_{max}) was informed by the depemokimab FTIH Study 205722 and the mepolizumab Phase 1 Study 204958 and is in line with results reported for monoclonal antibodies against soluble targets delivered subcutaneously.

Between subject variability (CV_b) of 30% was assumed for both AUC(0-inf) and C_{max}. Based on this CV_b, with a sample size of 63 participants per treatment group, the 90% CI for an estimated ratio of autoinjector versus PFS of 1.00 will be (0.92, 1.09).

In addition, assuming a within-subject correlation of 0.8 between AUC and C_{max}, and a true ratio of 1, a sample size of 63 participants will also provide 90% power to observe geometric CI of geometric mean ratio within the bioequivalence range of (0.8, 1.25) for both parameters.

Approximately 140 healthy participants will be enrolled (accounting for drop-out rate of 10% until Week 18) resulting in at least 126 evaluable participants (approximately 63 for each treatment group, 21 per injection anatomical site within each treatment group).

5.1. Sample Size Sensitivity

The table below provides the expected 90% CI estimates for a range of CV_b, assuming 5% difference in either direction in the ratio between autoinjector and PFS and n = 63 per treatment group.

CV_b	SDlogs	Estimated Ratio (Autoinjector/prefilled safety syringe)	Expected Two-sided 90% CI
0.30	0.293	0.95	(0.87,1.04)
		1.00	(0.92,1.09)
		1.05	(0.96,1.15)
0.35	0.339	0.95	(0.86,1.05)
		1.00	(0.90,1.11)
		1.05	(0.95,1.16)

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, 65-84 and >=85 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.

Past medical conditions and current medical conditions as of screening will be summarized as "Summary of Past and Current Medical Conditions".

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 concomitant medications taken during treatment.

6.1.5. Study Intervention Compliance

Not applicable

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)**
Haematocrit	Ratio of 1	Male	0.33	0.54
		Female	0.33	0.54
		Δ from BL	↓0.075	
Haemoglobin	g/L	Male	110	180
		Female	110	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	2.5
Reticulocyte	Fraction Of 1		0.005	0.025

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	umol/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	≥ 3x 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
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Absolute QT	msec		> 600
Change from Baseline			
Increase from Baseline QTcF	msec		> 60

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 Period

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

6.2.2.1. Treatment States for Safety Data

Treatment State	Definition
Pre-Treatment	Assessment/Event Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Assessment/Event Date ≤ Date of Last Dose of Study Treatment + 182 days
Post-Treatment	Assessment/Event Date > Date of Last Dose of Study Treatment + 182 days

6.2.2.2. Study Phases for Concomitant Medication

Study Phase	Definition
Pre-Treatment	Concomitant medication (CM) start date < Study Treatment start date (If the medication end date is not missing and is before 28 days prior to screening visit)
On-Treatment	If CM start date < Study Treatment start date and CM stop date ≥Study Treatment start date or If Study Treatment start date < CM start Date < Last Dose of Study Treatment date + 182 days
Post-Treatment	If CM start date < Last Dose of Study Treatment date +182 days and CM stop date ≥Last Dose of Study Treatment date +182 days Or If CM start Date > Last Dose of Study Treatment date +182 days

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

- If the AE start date is on or after study treatment start date and the study treatment stop date is missing, then the AE will be considered as on-treatment.
- Time of study Treatment dosing and start/stop time of AEs should be considered, if collected.

Study Phase	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ AE start date≤ Date of Last Dose + 182 days
Post-treatment	AE start date > Date of Last Dose + 182 days

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

Visit Slotting for Unscheduled and Withdrawal Visit

- Unscheduled/early withdrawal assessment will be slotted to its nearest scheduled, as per the SOA, nominal visit if:
- a) it is within 2 weeks of the nominal visit

b) the assessment is missing at that visit. That is if there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits

Otherwise, it will remain as unscheduled and will only be included in the listing if appliable.

- Data reported at the unscheduled/early withdrawal visit which has been re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit.

- Data reported at the unscheduled/early withdrawal visit which has not been re-assigned to a scheduled visit will not be included in analyses, summary tables and figures by scheduled visit.

- Data reported at the unscheduled/early withdrawal visit (either visit is re-assigned or not) will be included in the assessment of maximum or worst-case post-baseline summaries for any relevant endpoints, and all data will be included in listings.

- If all assessments within the same window are from unscheduled visits, the earliest one will be taken in the slotting. That is Unscheduled visits should be slotted so that the visit that is closest to the target day is slotted, and the other unscheduled visits remain unscheduled

- If there are two unscheduled visits that are equidistant from the target date of the same nominal visit, the latest unscheduled assessment should be slotted. The unscheduled visit that occurred before the target date should remain unscheduled.
- If there is an unscheduled visit that is equidistant from two nominal visits then the unscheduled visit should be slotted to the earlier of the two visits.
- Early withdrawal visits take precedent over unscheduled visits when it comes to slotting so that if there is both an early withdrawal visit and unscheduled visit that are within the required window for a nominal visit the early withdrawal visit will be slotted first and the unscheduled visit will remain unscheduled.

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 Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or 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 adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If month and year of start date = month and year of study intervention start date, then

– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

– Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

• If year of start date = year of study intervention start date, then

– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.

– Else set start date = study intervention start date.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td><table>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications</td><td>
Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If month and year of start date = month and year of study intervention start date, then

– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

– Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

• If year of start date = year of study intervention start date, then

– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.

– Else set start date = study. intervention start date.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Age</td><td>Age will be calculated based on the Pre-Screening Visit date (or Screening, if pre-screening not performed).</td></tr>
</table>

Element	Reporting Detail
	• 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. Early PK Access Key Activities

No formal interim analysis is planned; however, if recruitment is significantly slower than anticipated, then a single interim analysis may be conducted to assess variability, and which could result in a re-estimation of the sample size. Available PK concentration data from completed participants may be inspected to support development of depemokimab PK model. No changes to the conduct of the study will be implemented because of these analyses.

6.2.8. Abbreviations & Trademarks

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
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

Abbreviation	Description
C_{max}	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
PFS	Pre-filled Safety Syringe
PK	Pharmacokinetic
QTcF	QT Interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation	Description
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SSD	Safety Syringe Device
t½	Terminal Phase Half-life
tlast	Time of Last Quantifiable Concentration
T_{max}	Time of Occurrence of C_{max}
Vz/F	Apparent Volume of Distribution.
WBC	While Blood Cell

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HARP

Trademarks not owned by the [GlaxoSmithKline] Group of Companies
NONMEM
SAS
WinNonlin

7. REFERENCES

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, eds. Contraceptive technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.