Statistical Analysis Plan

Study ID: 212979

Official Title of Study: A Randomised, Double-blind, Placebo-controlled Study of the Safety,Tolerability, Pharmacokinetics, Target Engagement and Immunogenicity of a single subcutaneous dose of GSK3858279 administered to Healthy Caucasian, Chinese and Japanese Participants.

Date of Document: 28-NOV-2022

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Randomised, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Pharmacokinetics, Target Engagement and Immunogenicity of a single subcutaneous dose of GSK3858279 administered to Healthy Caucasian, Chinese and Japanese Participants.

Study Number: 212979

Compound Number: GSK3858279

Abbreviated Title: Safety, tolerability, pharmacokinetics and target engagement of GSK3858279 after a single subcutaneous dose in healthy Caucasian, Chinese and Japanese participants

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s) TBC

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	10 May 2022	Protocol Amendment 02 (29-APR-2022)	Not Applicable	Original version
SAP Amendment 1	28 Nov 2022	Protocol Amendment 02 (29-APR-2022)	Update to Objectives and Endpoints table	Changes to objectives not made in original version following protocol amendment 2
			Removal of sentence specifying Anatomical Therapeutic Chemical (ATC) classifications will not appear in summaries	Decision to include ATC classifications in summaries
			Inclusion of details of additional interim analysis	Decision made to conduct additional interim analysis for this study to support regulatory submissions

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 212979.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single SC dose of GSK3858279 compared with placebo administered to healthy participants including cohorts of Japanese, Chinese and Caucasians	• Incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs • Occurrence of clinically important changes from baseline in clinical laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs (blood pressure, heart rate, body temperature), and cardiac parameters (electrocardiogram)
• To assess the pharmacokinetic (serum PK) profile up to 56 days following a single SC dose of GSK3858279 in healthy participants including cohorts of Japanese, Chinese and Caucasians	• PK parameters: area under the concentration-time curve (AUC(0-56), AUC(0-t) post-dose), time of occurrence of last quantifiable concentration (tlast), maximum observed concentration (Cmax), and time of occurrence of Cmax (tmax) per cohort as data permits
Secondary	
• To evaluate target engagement (TE) up to 56 days following a single SC dose of GSK3858279 in healthy participants including cohorts of Japanese, Chinese and Caucasians.	• Reduction (%) from baseline in free CCL17: maximum, minimum and at Days 7, 14, 28 and 56 post-dose • Total CCL17 (free and when bound to GSK3858279): maximum observed concentration (Cmax), time of Cmax (tmax), maximum fold increase compared to baseline, fold increase compared to baseline at Days 7, 14, 28 and 56 post-dose.
• To assess the potential for anti-drug	• Incidence of pre-existing ADAs

Objectives	Endpoints
antibody (ADA) formation	• Incidence of treatment-emergent ADAs over time (and whether neutralising)
Exploratory	

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1.2. Study Design

Overview of Study Design and Key Features
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Design Features	• This is a Ph1 Randomised, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Pharmacokinetics, Target Engagement and Immunogenicity of a single subcutaneous dose of GSK3858279 administered to Healthy Caucasian, Chinese and Japanese Participants. • The total duration of this study is not expected to exceed a maximum of CCI [redacted]: (Screening [up to 28 days] and a follow-up period of CCI [redacted]. Follow-up may be extended if a serious or clinically significant AE CCI [redacted]. • The primary PK and TE analysis for this study will occur once all participants have completed Day 57. An interim analysis of safety will also be conducted at this time.
Study intervention	Study intervention will be administered on Day 1 as four separate SC injections of either GSK3858279 (CCI [redacted] or Placebo.
Study intervention Assignment	Cohorts of Caucasian, Chinese and Japanese participants will be randomised to GSK3858279 CCI [redacted] or Placebo in a 7:3 ratio, respectively for each cohort.
Interim Analysis	Interim analysis of Safety data will occur alongside primary PK and TE analysis at Day 57. Additional interim analyses may be performed on data assessed in an unblinded manner, to support regulatory submissions. No changes to the conduct of the study will be implemented as a result of the analyses.

2. STATISTICAL HYPOTHESES

The co- primary objectives of this study are:

- To evaluate the safety and tolerability of a single SC dose of GSK3858279 compared with placebo administered to healthy participants including cohorts of Japanese, Chinese and Caucasians
- To assess the pharmacokinetic (PK) profile of a single SC dose of GSK3858279 in healthy participants including cohorts of Japanese, Chinese and Caucasians

No formal statistical hypotheses will be tested.

2.1. Multiplicity Adjustment

There will be no adjustments for multiplicity.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All participants who entered the study, signed the ICF and were eligible for randomisation (regardless of whether the participant went on to be randomised). 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
Randomised	All participants who were randomly assigned to study intervention in the study. Data will be reported according to the randomised study intervention.	Study Population
Safety	All participants who received at least one injection of study intervention. Data will be reported according to the actual study intervention received.	Safety
Pharmacokinetic (PK)	All participants in the safety population who received an active dose of study treatment and had at least one reportable PK assessment (Non-quantifiable [NQ] values will be considered as reportable values). Participants will be analysed according to the study intervention they actually received.	PK
Target Engagement (TE)	All participants in the safety population who had at least one reportable TE assessment (Non-quantifiable [NQ] values will be considered as reportable values). Participants will be analysed according to the study intervention they actually received.	TE

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who withdraw from the study may be replaced, with any replacements beginning from the start of the study.

Summary tables will provide the following descriptive statistics as a minimum, unless otherwise specified:

- Continuous data (normally distributed):
  n, mean, standard deviation (SD), median, minimum and maximum.

- Continuous data (log-normally distributed):
  n, geometric mean, SD on the log scale (SD (log)), median, minimum and maximum.

- Categorical data:
  number and percentage of participants in each category.

4.1.2. 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.

The CCL17 levels (free, total) baseline value will be derived by averaging the two pre-dose measurements (Day -2 and Day 1 pre-dose).

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

4.2. Primary Endpoints Analyses

The primary endpoints for this study are:

- Incidence of AEs, SAEs, withdrawals due to AEs

- Occurrence of clinically important changes from baseline in clinical laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs (blood pressure, heart rate, body temperature), and cardiac parameters (electrocardiogram)

- PK parameters: area under the concentration-time curve (AUC(0-56), AUC(0-t)), time of occurrence of last quantifiable concentration (tlast), maximum observed

concentration (Cmax), and time of occurrence of Cmax (tmax) per cohort as data permits

4.2.1. Pharmacokinetics

All PK analyses will be performed on the PK population. Serum GSK3858279 concentration-time data will be analysed by non-compartmental and/or model-based methods, as appropriate. Calculations will be based on the actual sampling times recorded during the study. Concentration-time data will be listed for each participant and summarized by planned time point and cohort. The following summary statistics will be calculated for each cohort:

- Geometric mean, 95% CI of the geometric mean, SD(log), median , min and max

Individual serum concentration-time data and summary data will be graphically displayed.

From the serum concentration-time data collected up to Day 57, the following PK parameters will be determined, as data permit:

- Area under the serum concentration-time curve (AUC(0-56), AUC(0-t))
- Time of last quantifiable concentration (tlast)
- Maximum observed concentration (Cmax)
- Time of occurrence of Cmax (tmax)

4.2.1.1. Summary Measures of Derived Parameters

PK parameters will be listed for each participant and summarized descriptively by cohort. For each of these parameters, except for tmax and tlast, the following summary statistics will be calculated for each cohort:

- Median, maximum, minimum, arithmetic mean and standard deviation of non-transformed data.
- Geometric mean, 95% confidence interval (CI) for the geometric mean, standard deviation and coefficient of variation of logarithmically transformed data.

For tmax and tlast, arithmetic mean, standard deviation, median, maximum and minimum will be calculated.

4.2.1.2. Statistical Analysis

Table 1 Statistical Analysis of Primary Endpoint(s)

Endpoint
• AUC(0-56) • Cmax
Model Specification
• The PK parameters will be $\log_e$ transformed and analysed using a mixed model. • Terms fitted in the model will include ethnicity and $\log_e$(body weight). • An additional model including the ethnicity term only will be fitted.
Model Checking & Diagnostics
• Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model, respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Model Results Presentation
• Geometric mean and 90% CIs will be calculated for each of the ethnic cohorts. • Comparisons for Japanese/Caucasians and Chinese/Caucasians will also be presented – this will be determined as differences on the $\log_e$ scale back transformed to present as ratios.

4.2.2. Safety

The following primary safety endpoints will be summarised descriptively by ethnic cohort and treatment group, as described in Section 4.5:

- Incidence of adverse events (AEs)
- Serious adverse events (SAEs)
- Withdrawals due to AEs

- Occurrence of clinically important changes from baseline in clinical laboratory parameters, vital signs and ECGs

4.2.3. Sensitivity analyses

No formal sensitivity analyses are planned.

4.3. Secondary Endpoint(s) Analyses

The secondary endpoints for this study are:

- Reduction (%) from baseline in free CCL17: maximum, minimum and at Days 7, 14, 28 and 56 post-dose
- Total CCL17 (free and when bound to GSK3858279): maximum observed concentration (Cmax), time of Cmax (tmax), maximum fold increase compared to baseline, fold increase compared to baseline at Days 7, 14, 28 and 56 post-dose.
- Incidence of pre-existing ADAs
- Incidence of treatment-emergent ADAs over time (and whether neutralising)

4.3.1. Target Engagement

All TE analyses will be performed on the TE population. Calculations will be based on the actual sampling times recorded during the study.

Free and total CCL17 concentration-time data will be listed for each participant and summarized by planned time point and cohort.

For Free CCL17, Total CCL17 and Total CCL17 Fold Increase parameters, the following summary statistics will be calculated for each cohort:

- Geometric mean, 95% CI of the geometric mean, SD(log), median, min, and max

For Free CCL17 Percentage Reduction parameter, the following summary statistics will be calculated for each cohort:

- Geometric mean, 95% CI of the geometric mean, SD(logit), median, min, and max

Individual serum concentration-time data and summary data will be graphically displayed.

From the serum concentration-time data collected up to Day 57, the following target engagement parameters will be derived, as data permit:

- Baseline for free and total CCL17
- Percentage reduction from baseline in free CCL17 by time point (Days 7, 14, 28 and 56 post-dose)
- Minimum and maximum percentage reduction from baseline in free CCL17
- Cmax and tmax for total CCL17
- Fold increase compared to baseline for total CCL17 by time point
- Maximum fold increase compared to baseline for total CCL17

4.3.1.1. Summary Measures of Derived Parameters

TE parameters will be listed for each participant and summarized descriptively by cohort. For each of these parameters, the following summary statistics will be calculated for each cohort:

- Median, maximum, minimum, arithmetic mean and standard deviation of non-transformed data.
- Geometric mean, 95% CI for the geometric mean, standard deviation and coefficient of variation of logarithmically transformed data.
- Geometric mean, 95% CI for the geometric mean and standard deviation of logit transformed data. A logit-transformation will be used for the percentage reduction (including minimum and maximum) parameter.

For tmax, arithmetic mean, standard deviation, median, maximum and minimum will be calculated.

4.3.2. Anti-drug antibody (ADA) formation

The incidence of pre-existing ADAs and the incidence of treatment-emergent ADAs over time (and whether neutralising) will be summarised descriptively.

4.3.3. Sensitivity analyses

No formal sensitivity analyses are planned.

4.4. Exploratory Endpoint Analyses

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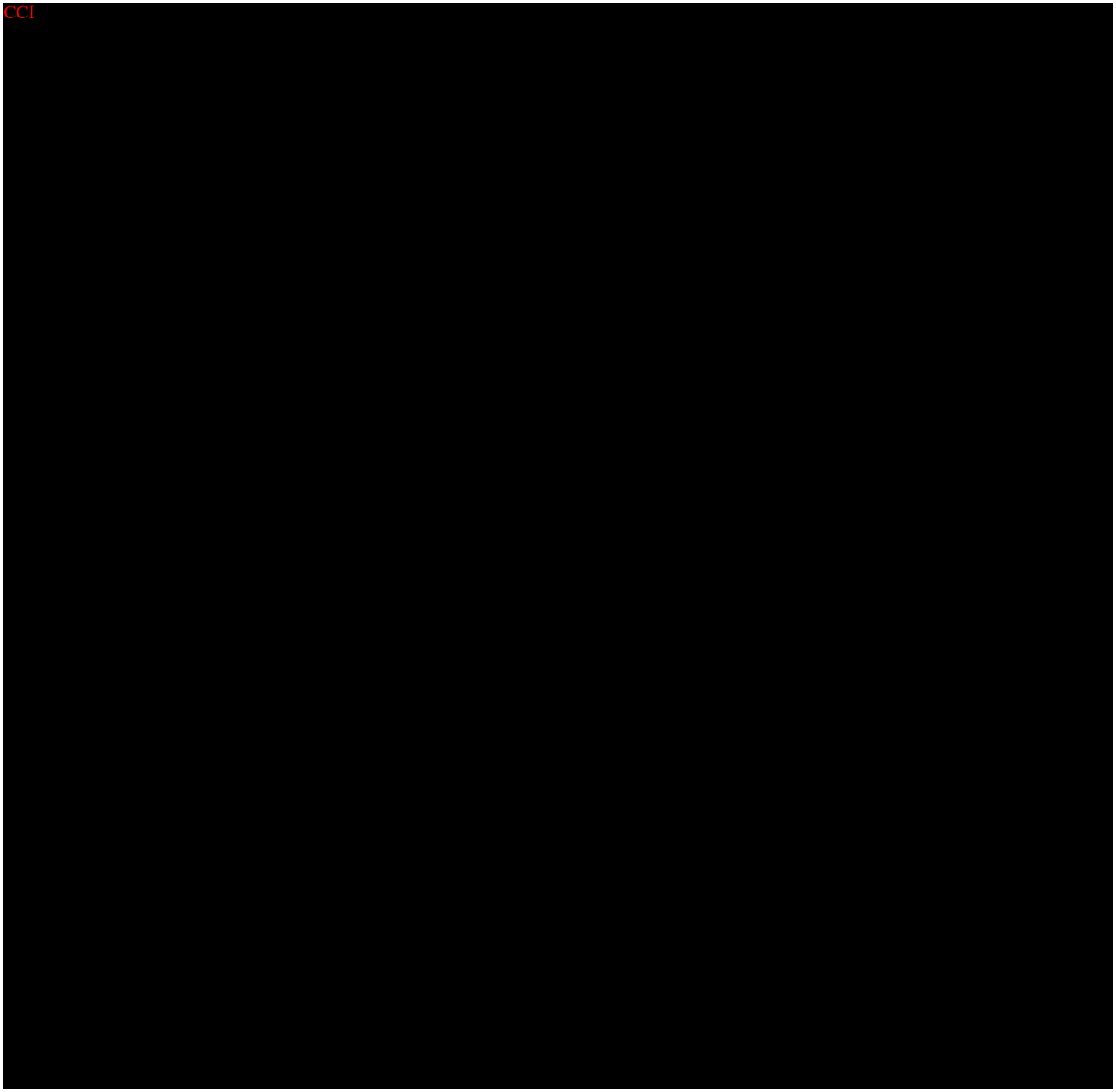

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4.5. Safety Analyses

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

Safety data will be presented by ethnic cohort and treatment group.

4.5.1. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date. All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not. All AE and SAE summaries will be by preferred term (PT) and System Organ Class (SOC).

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

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, mild, moderate, or severe AEs, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced.

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”. 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.

4.5.1.1. Adverse Events of Special Interest

There are no adverse events of special interest identified for this study.

4.5.1.2. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The incidence of AEs and SAEs of COVID-19, COVID-19 AEs leading to study intervention discontinuation, COVID-19 AEs leading to study withdrawal, and severe COVID-19 AEs at individual PT level can be obtained from the standard AE/SAE summaries.

COVID-19 assessments for participants with COVID-19 AEs will be summarized.

If >25% participants in any given cohort report ≥1 COVID-19 AE, then onset and duration of the first occurrence of COVID-19 AEs, and COVID-19 AE symptoms (from the COVID-19 eCRF page) will be summarized. The same rule will apply to COVID-19 SAEs.

4.5.2. Additional Safety Assessments

4.5.2.1. Laboratory Data

Summaries of worst-case changes from baseline with respect to Potential Clinical Importance (PCI) Criteria will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

Separate summary tables for haematology, and chemistry laboratory tests will be produced. Liver function laboratory tests will be included with chemistry lab tests.

4.5.2.2. Vital Signs

A summary of change from baseline vital sign values will be provided by visit and treatment group, including systolic blood pressure, diastolic blood pressure, heart rate and temperature.

Summaries of vital sign results relative to PCI criteria will also be provided. The summary will include baseline, planned visit and worst-case post baseline.

4.5.2.3. ECG

The baseline ECG will be taken as the mean of the triplicate values collected pre-dose on Day 1. The following will be summarised by visit: ECG findings and change from baseline in ECG values.

The number of subjects with maximum QTc values at baseline and post-baseline relative to baseline will be summarized using the following categories: No Change or Decrease To <=450, Any Increase >450, Increase To >450 to <=480, Increase To >480 to <=500, and Increase To >500.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: Increase of <= 30, 31-60 and >60 msec. A summary of change in QTc value will display the number and percentage of subjects with a change within each range for the worst-case post-baseline only. Subjects with missing baseline values will be excluded from this summary.

4.6. Other Analyses

4.6.1. Subgroup analyses

No formal subgroup analyses are planned.

4.7. Interim Analyses

The GSK Biostatistics Team (including Third Party Suppliers) and GSK CPMS Team (including Third Party Suppliers) will be unblinded to all subjects already randomised at the time of the interim analyses and will process and analyse the data.

Results (group summaries and if required, individual summaries) may be shared internally within GSK as deemed necessary to inform the clinical development plan and prepare supporting documents for the potential phase 2 study. Data from the interim analyses may also be shared externally with regulators (e.g., via an interim CSR) as required to support the potential phase 2 study.

Until the time of the primary PK and TE analysis (all participants completed Day 57), access to the results for interim analyses conducted at an earlier timepoint (excluding CPMS and Biostatistics) will be documented in a separate document which will detail the individuals or groups within GSK who reviewed the data (i.e. name and function, type of data, purpose and date). This document will be stored in the TMF.

No changes to the conduct of the study will be implemented as a result of the interim analyses.

4.7.1. Day 57 Analysis

Alongside the primary PK and TE analysis, an interim analysis of safety data will occur once all participants have completed Day 57. The planned interim analyses will be performed as detailed in Section 4.5 with the full list of outputs being produced specified in the OPS.

This data will be assessed in an unblinded manner and used to support regulatory submissions. No changes to the conduct of the study will be implemented as a result of the interim analyses.

As the primary purpose of the interim analyses is to provide safety data alongside primary PK data to regulators – to support China and Japan's potential participation in GSK3858279's phase 2 programs – data at both an individual and aggregate treatment group level will be provided.

4.7.2. Other

Prior to the primary PK and TE analysis, an additional interim analysis including Study Population, Safety, TE and PK data may be performed to support regulatory submissions. The data will be assessed in an unblinded manner. No changes to the conduct of the study will be implemented as a result of the interim analyses.

This interim analysis will occur on all available data at a specified timepoint. This timepoint will be decided by the central study team in conjunction with the Chinese and Japanese LOCs.

As the primary purpose of the interim analyses is to provide Safety and PK data to regulators – to support China and Japan's potential participation in GSK3858279's phase 2 programs – data at both an individual and aggregate treatment group level will be provided.

The full list of outputs being produced by the GSK Biostatistics Team (including Third Party Suppliers) for inclusion in this interim analysis are detailed in the OPS. GSK CPMS Team (including Third Party Suppliers) will produce additional outputs as appropriate.

4.8. Changes to Protocol Defined Analyses

The protocol specified that interim analysis details, including what data will be reviewed, the level of unblinding and who will have access to the data, would be documented in an interim charter. This information has been included in Section 4.7 and a separate interim analysis charter will not be produced.

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 2

Table 2 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Section 9.2.3: "Primary analysis will be performed on the PK parameters AUC (0-56) post-dose and Cmax. The parameters will be log_e transformed and then analysed using a mixed model, with ethnicity and body weight included as covariates. Geometric mean and 90% confidence intervals will be calculated for each of the ethnic cohorts, along with the comparisons for Japanese/Caucasians and Chinese/Caucasians."	Section 4.2.1.2: "The PK parameters will be log_e transformed and analysed using a mixed model. Terms fitted in the model will include ethnicity and log_e(body weight). An additional model including the ethnicity term only will be fitted."	• Inclusion of additional analysis without body weight to be presented alongside the original model • Inclusion of log_e(bodyweight) instead of bodyweight as linear relationship expected between PK parameters and log_e (bodyweight)

5. SAMPLE SIZE DETERMINATION

Approximately 10 participants are to be randomized (7 active: 3 placebo) per cohort to ensure that a minimum of 6 participants on active and 2 on placebo per cohort are evaluable. An evaluable participant is one that has been dosed and has safety and all PK data up to Day 57. Replacements (assigned to the same treatment) are permitted at the discretion of the sponsor in consultation with the investigator.

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

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

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 will be summarized. For those who have neither completed nor withdrawn, they will be categorized as ongoing. A participant is considered to have completed the study if they have completed all planned study assessments including the follow-up visit.

Rescreening of screen failures is allowed as per protocol. Rescreened participants will be summarized under their latest participant number.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening, Body Mass Index (BMI) 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 Enrolled Analysis Set.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized and include overall important protocol deviations, COVID-19 related important protocol deviations and non COVID-19 related important protocol deviations.

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 unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be summarized in both a table and a figure.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only. The summary of concomitant medications will be provided by ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary.

Prior medication is any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest without missing end date and with end date >7 days prior to dosing.

Concomitant medication is any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest, that is not considered prior.

6.1.5. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be summarized.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

6.2.1.1. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110
Body Temperature	°C	≤ 35.5	>38.0

6.2.1.2. Laboratory Values

Haematology				
Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
Hematocrit	Ratio of 1	Male	0.39	0.54
		Female	0.35	0.49
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male	124	180
		Female	109	180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.75	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		2.5	20

Clinical Chemistry				
Laboratory 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			1.3 X ULN
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO_2	mmol/L		18	32
Creatinine Kinase	mg/dL			>1.6 X ULN
C-reactive Protein	mg/L			≥3.0
Troponin T	ng/ml			14.1
NT-pro BNP	ng/L			125.99

Urinalysis
A subject is considered to have urinalysis results of PCI, if they have abnormal microscopic examination.

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	IU/L	High	≥2xULN
AST/SGOT	IU/L	High	≥2xULN
AlkPhos	IU/L	High	≥2xULN
T Bilirubin	µmol/L	High	≥1.5xULN
T. Bilirubin + ALT	µmol/L IU/L	High	ALT≥3xULN AND bilirubin≥ 1.5xULN

6.2.1.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		>500
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>120
Change from Baseline			
Increase from Baseline QTc	msec		>60

6.2.2. Study Phase

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the single dose of study intervention.

On-Intervention is defined as time following single dose. If time of assessment (e.g. ECG, Lab, vital signs) is not collected and assessment date is the same as the dose date, the assessment is considered pre-intervention. If time of study intervention (e.g. AE, concomitant medication) is not collected and the start/end date is the same as dose date, it is considered on-intervention.

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 Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

For data summaries by visit, scheduled visits with nominal visit description as well as the worst-case post baseline will be displayed. Unscheduled visits will not be displayed or slotted into a visit window but will be included in the derivation of worst-case post baseline assessment. All unscheduled visits will be displayed in the listing.

6.2.5. Multiple measurements at One Analysis Time Point

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.

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).</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:

o 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 =</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td></td><td></td><td>January 1.

Else if study intervention start date is not missing:

o 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></td><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></td><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td></td><td>Completely missing start/end date</td><td>No imputation</td></tr>
<tr><td>Concomitant Medications/ Medical History</td><td colspan="2">• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</td></tr>
<tr><td></td><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:

o 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></td><td>Missing start</td><td>If study intervention start date is missing (i.e.</td></tr>
</table>

Element	Reporting Detail		
	day and month	participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: o 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.	
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).	
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.	
	Completely missing start/end date	No imputation	

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7. REFERENCES

GlaxoSmithKline Document Number TMF-14343601. Project Data Analysis Plan for an Integrated Analysis of GSK3858279 Pharmacokinetic/Target Engagement/Pharmacodynamic relationship in Healthy Participants, Participants with Osteoarthritis of the Knee and other Indications. Effective Date 30-Dec-2021