Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for GSK2831781 study 207823: A randomised, double-blind, placebo-controlled Phase I study of the safety and tolerability, pharmacokinetics, and pharmacodynamics of a single intravenous dose of GSK2831781 in healthy Japanese and Caucasian participants, and a single subcutaneous dose of GSK2831781 in healthy Caucasian participants.
Compound Number	:	GSK2831781
Effective Date	:	01-OCT-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2018N393275_01 of study 207823.
- This RAP is intended to describe the safety, tolerability, pharmacokinetics and pharmacodynamics analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Interim Analysis (IA) and Statistical Analysis Complete (SAC) deliverables.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2018N393275_01	06-MAY-2019	Amendment 1
2018N393275_00	13-MAR-2019	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 7.3 of the Protocol: a single Treatment Group B is defined for the active 150 mg SC dose.	• Section 2.3 and Section 5.2 of the RAP: the active 150 mg SC dose in Part B corresponds to 3 treatment groups, coded B1, B2 and B3.	• As described in the RCCS document, the randomised allocation of active dose to syringe 1, 2 or 3 is performed as part of the main randomisation effort.

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability after single IV dosing of GSK2831781 in healthy Japanese and Caucasian participants, and SC dosing in healthy Caucasian participants	• AEs, vital signs, clinical laboratory values (haematology, clinical chemistry, and urinalysis), 12-lead ECG • Local tolerability
Secondary	
• To evaluate the PK of GSK2831781 after a single IV dose in healthy Japanese and Caucasian participants (Part A)	• GSK2831781 PK parameters following single IV dose: area under the plasma concentration-time curve [AUC(0-t)], maximum observed plasma concentration (Cmax), time of occurrence of Cmax (tmax)
• To evaluate the PK of GSK2831781 after a single SC dose in healthy Caucasian participants (Part B)	• GSK2831781 PK parameters following single SC dose: AUC(0-t), Cmax, tmax, bioavailability (F)

Objectives	Endpoints
• To evaluate the effect of a single IV or SC dose of GSK2831781 on depletion of $LAG3^+$ T cells in blood	• PK/PD relationship between plasma PK of GSK2831781 and $LAG3^+$ T cells in blood over time
• To investigate the immunogenicity of single IV and SC doses of GSK2831781	• ADAs over time
Exploratory	
• To evaluate the concentration-time profiles of GSK2831781 after a single IV dose in healthy Japanese and Caucasian participants (Part A)	• GSK2831781 PK concentrations over time following single IV dose
• To evaluate the concentration-time profiles of GSK2831781 after a single SC dose in healthy Caucasian participants (Part B)	• GSK2831781 PK concentrations over time following single SC dose
• To evaluate the effect of a single IV or SC dose of GSK2831781 on soluble LAG3 (sLAG3) concentrations	• Soluble LAG3 (sLAG3) concentrations in blood over time
• To evaluate the effect of GSK2831781 on regulatory T cells in blood	• PK/PD relationship between plasma PK of GSK2831781 and regulatory T cells in blood over time

2.3. Study Design

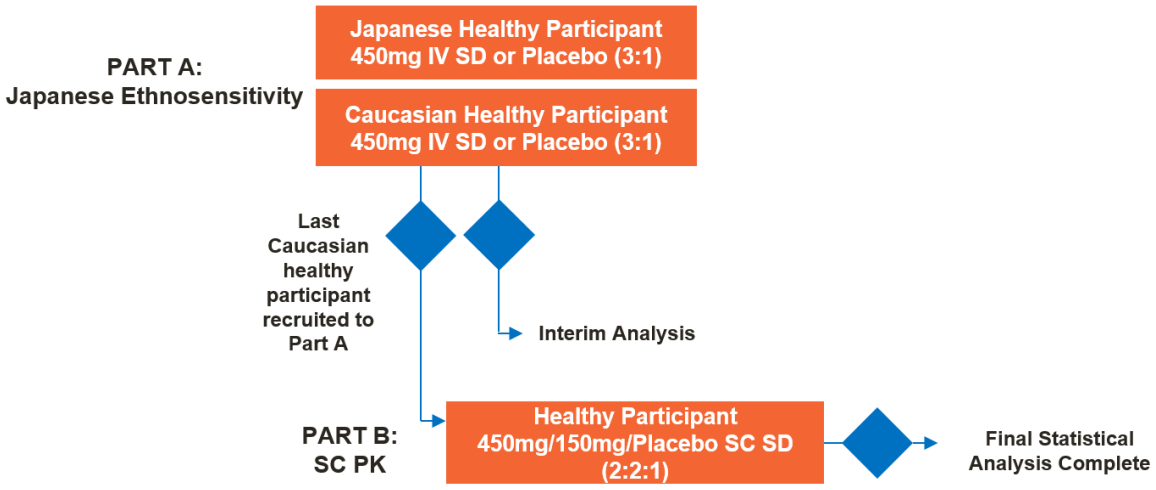
This study is a double-blind, placebo-controlled, randomised, parallel group, two-part study, with single IV doses administered to healthy Japanese and Caucasian participants, or SC doses administered to healthy Caucasian participants.

In Part A, single IV doses of 450 mg GSK2831781 or placebo will be administered to Japanese or Caucasian healthy participants, with stratification by ethnicity.

In Part B, single SC doses of 150 mg or 450 mg GSK2831781, or placebo, will be administered to healthy Caucasian participants.

At least one interim analysis will be conducted during the study (see Section 3.1 for further details).

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT) (which will include a subset of the 207823 study team) will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

Study Schematic


Part A: Overview of Study Design and Key Features	
Part A Design Features	• Part A will be a single centre, parallel group, single dose part. It is designed to investigate whether there are any differences due to ethnicity in safety and tolerability, or PK and PK/PD relationship in blood between healthy Japanese and Caucasian participants following a single IV 450 mg dose of GSK2831781. • Separate cohorts of participants will be enrolled into Parts A and B. • Part A will consist of a single cohort of 16 healthy participants, stratified by ethnicity: 8 participants will be Japanese and 8 will be Caucasian. Up to a maximum of 32 participants may be enrolled if a dose reduction is needed. • The participants in each ethnicity stratum will be randomised in a 3:1 ratio to receive either 450 mg GSK2831781 IV or placebo. If a dose reduction is needed, the new participants in each ethnicity stratum will also be randomised in a 3:1 ratio to receive either GSK2831781 IV or placebo. • Part A study duration, including screening and follow-up, is not expected to exceed 147 days for any participant.
Part A Dosing	• Participants will be dosed once on day 1. • In Part A, in order to bridge from the first-time-in human study (GSK Study 200630), dosing episodes will initially be separated by a minimum of 22 hours, until 3 participants in one of the strata have been dosed and monitored for a minimum of 46 hours. Subsequently, the remaining participants in Part A will be dosed, unless stopping criteria have been met.
Part A Time & Events	• Refer to Appendix 2.
Part A Treatment Assignment	• Participants will be assigned to either 450mg GSK2831781 IV or placebo in a 3:1 ratio, stratified by ethnicity. The treatment codes will be:

Treatment code	Treatment Description
A	450 mg GSK2831781 IV
P	Placebo IV

Part A: Overview of Study Design and Key Features	
	• If a dose reduction is needed, the new participants in each ethnicity stratum will also be randomised in a 3:1 ratio to receive either GSK2831781 IV or placebo, according to the randomisation schedule.
Part A Interim Analysis	• An interim analysis for Part A will be performed once at least 8 participants in each stratum have completed their Day 8 visit, and at least 6 participants in each stratum have completed their Day 29 visit, where Safety, PK and PD data will be reviewed. • See Section 3.1 for further details.

Part B: Overview of Study Design and Key Features	
Part B Design Features	• Once the final Caucasian participant is recruited into Part A of the study, recruitment to Part B may commence. • Part B will be a single centre, parallel group, single dose part. It is designed to explore the safety and tolerability, PK and PK/PD relationship in blood following a single dose of SC GSK2831781 at 150 mg and 450 mg dose levels, or placebo, in healthy Caucasian participants. • As the 450 mg dose level requires 3 injections of GSK2831781 150 mg, participants randomised to the 150 mg dose level or placebo will also receive 3 injections (using 0.9% saline placebo as dummy injections, where needed) to maintain the blind. In the 150 mg case, the allocation of active GSK2831781 to one of the three syringes will be randomised. • Separate cohorts of participants will be enrolled into Parts A and B. • Part B will consist of a single cohort of 20 healthy Caucasian participants. Up to a maximum of 30 participants may be enrolled if a dose reduction is needed. • The participants will be randomised in a 2:2:1 ratio to receive 150 mg GSK2831781 SC, 450 mg GSK2831781 SC, or placebo. • The 8 planned 150 mg participants will be randomly allocated active syringe 1, 2 or 3 in a 3:3:2 ratio. • Part B study duration, including screening and follow-up, is not expected to exceed 147 days for any participant.
Part B Dosing	• Participants will be dosed once on day 1. • In Part B, as this will be the first experience with SC administration in humans, sentinel dosing will take place: the first two participants dosed will be randomised so that 1 participant will receive 150 mg GSK2831781 and 1 will receive placebo.
Part B Time & Events	• Refer to Appendix 2.
Part B Treatment Assignment	• Participants will be assigned to 150 mg GSK2831781 SC or 450 mg GSK2831781 SC or placebo in a 2:2:1 ratio. The treatment codes will be:

Treatment code	Treatment Description
B1	150 mg GSK2831781 SC injection 1 active
B2	150 mg GSK2831781 SC injection 2 active
B3	150 mg GSK2831781 SC injection 3 active

Part B: Overview of Study Design and Key Features		
	C	450 mg GSK2831781 SC
	Q	Placebo SC
Part B Interim Analysis	• No interim analyses will be performed during Part B.	

2.4. Statistical Analyses

The primary objective of this study is to determine the safety and tolerability of a single intravenous dose of GSK2831781 in healthy Japanese and Caucasian participants, and a single subcutaneous dose of GSK2831781 in healthy Caucasian participants. No formal hypotheses will be tested.

An estimation approach will be used to describe pharmacokinetics of GSK2831781, where point estimates and corresponding 90% confidence intervals will be constructed, unless otherwise stated.

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim analysis for Part A will be performed once at least 8 participants in each stratum have completed their Day 8 visit, and at least 6 participants in each stratum have completed their Day 29 visit, where Safety, PK and PD data will be reviewed. The interim analysis will be utilised to determine if Japanese participants can be recruited into the Phase 2 study (204869) under the existing dosing strategy.

An Interim Data Review Committee (DRC) will be utilised in this study to review the interim analysis data. The DRC will be composed of a limited number of people, who may be members of the 207823 study team, including the statistician, a senior safety representative, lead physician and the pharmacokineticist. A DRC Charter will contain the details regarding the DRC, including membership, decision rules for the interim, and required data integrity and data quality control.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in Section 5.4 of the protocol: the end of the study is defined as the date of the last visit (including follow-up) of the last participant in the study (Parts A and B).
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) have been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Description	Analyses Evaluated
Screened	All participants who were screened for eligibility.	• Study Population (specific only)
Randomized	All participants who are randomised into the study and receive a randomisation number.	• Study Population (specific only)
Safety	All Randomized participants who receive study intervention. Participants will be analysed according to the intervention they actually received.	• Study Population • Safety • PD • PK/PD
Pharmacokinetic (PK)	All Safety participants for whom a PK sample was obtained and analysed. Participants will be analysed according to the intervention they actually received.	• PK

Refer to Appendix 12: List of Data Displays which details the population used for each display.

Note that a participant is considered evaluable if they have been dosed and have safety and PK data up to Day 29 (Parts A and B).

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

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

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This output will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. General

Parts A and B will be reported separately, with separate outputs generated for each, unless stated otherwise.

5.2. Study Treatment & Sub-group Display Descriptors

In the Tables, Listings and Figures (TLF), treatment should be presented with placebo first, then in order of increasing dose within each part.

Part A: Treatment Groups Descriptions			
Randall NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	450 mg GSK2831781 IV	450 mg GSK2831781 IV	2
P	Placebo IV	Placebo IV	1

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. 450 mg GSK2831781 IV vs Placebo IV

A subset of Part A data displays will be presented with a combination of treatment groups and geographic ancestry stratification, as described in Section 5.4.

Part B: Treatment Groups Descriptions			
Randall NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
B1	150 mg GSK2831781 SC injection 1 active	150 mg GSK2831781 SC injection 1	2 (*)
B2	150 mg GSK2831781 SC injection 2 active	150 mg GSK2831781 SC injection 2	3 (*)
B3	150 mg GSK2831781 SC injection 3 active	150 mg GSK2831781 SC injection 3	4 (*)
C	450 mg GSK2831781 SC	450 mg GSK2831781 SC	5
Q	Placebo SC	Placebo SC	1

(*) Note that treatment groups B1, B2 and B3 will be combined into a single "150 mg GSK2831781 SC" group in most tables, figures and listings. Only a small subset of outputs, including listings of injection site reactions (Section 15.12 for details), will report B1, B2 and B3 as separate treatment groups.

Treatment comparisons will be displayed as follows using the descriptors as specified, where "150 mg GSK2831781 SC" includes treatment groups B1, B2 and B3:

1. 150 mg GSK2831781 SC vs Placebo SC
2. 450 mg GSK2831781 SC vs Placebo SC

5.3. Baseline Definitions

- The baseline value (in both Parts A and B) 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 dosing and used as baseline.
- Replicate assessments at a timepoint will be averaged, and the mean value will be used.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.4. Examination of Strata

The list of strata may be used in descriptive summaries and statistical analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details

Strata	• Part A: stratification by geographic ancestry (Caucasian vs Japanese).
	• Used for ethnosensitivity comparisons.
	• A subset of Part A data displays will be presented with the following groups, in this order:
	  ○ Placebo (Caucasian)
	  ○ Placebo (Japanese)
	  ○ 450 mg GSK2831781 (Caucasian)
	  ○ 450 mg GSK2831781 (Japanese)

5.5. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
15.3	Appendix 3: Assessment Windows
15.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
15.5	Appendix 5: Data Display Standards & Handling Conventions
15.6	Appendix 6: Derived and Transformed Data
15.7	Appendix 7: Reporting Standards for Missing Data
15.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

The study population analyses will be based on the Safety population, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. EFFICACY ANALYSES

There are no efficacy analyses to be included in this study.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

The definition of an AE is detailed in Appendix 3 of the protocol.

Analyses of AEs will include those events that are Treatment Emergent as defined in Section 15.4.

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and Liver function tests will be based on GSK Core Data Standards.

Clinical laboratory summaries will include all assessments post-baseline. All clinical laboratory assessments, including pre-baseline (i.e. screening), will be listed.

The details of the planned displays are in Appendix 12: List of Data Displays.

The laboratory assessments for each category are displayed below (Table 1 in Section 11.2 of the protocol):

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count Red Blood Cell (RBC) Count Haemoglobin Haematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Haemoglobin (MCH) %Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine Estimated Glomerular Filtration Rate (eGFR)	Sodium	Alanine Aminotransferase (ALT/Serum Glutamic-Pyruvic Transaminase	Total Protein

Laboratory Assessments	Parameters			
			(SGPT)	
	Glucose [non-fasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests (not to be reported)	• Breath alcohol screen • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology: HIV antibody, HbsAg, HbcAb, HCV antibody, EBV antibody[3], CMV antibody[3], VZV antibody[3] • Quantiferon test for TB			

NOTES:
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.2.3 of the protocol. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. To be repeated in event of possible viral reactivation.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

The non-laboratory safety test results include:

- ECGs
- Vital signs
- Local tolerability

The details of the planned displays are presented in Appendix 12: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

9.1. Endpoint / Variables

9.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 15.5.3 Reporting Standards for Pharmacokinetic).

9.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times.

Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits. Additional parameters may be included as required.

Parameter	Parameter Description
AUC(0-t)	• Area under the concentration-time curve from time zero to the time of last quantifiable concentration (C(t)). • Calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	• Maximum observed concentration. • Determined directly from the concentration-time data.
tmax	• Time to reach Cmax. • Determined directly from the concentration-time data.

9.2. Summary Measure

Descriptive statistics (n, arithmetic mean, standard deviation [SD], 95% CI, minimum, median and maximum) will be calculated by treatment (and geographic ancestry in Part A) for all PK concentrations over time and for the derived PK parameters. In addition, for log-transformed PK parameter variables, geometric mean, 95% CI and $\%CV_b$ will be provided.

9.3. Population of Interest

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.4. Strategy for Intercurrent (Post-Randomization) Events

A 'While on-study' strategy will be implemented for intercurrent events.

- Withdrawn participants may be replaced in the study. Replacement participants will be dosed with the planned treatment of the withdrawn participant.

- All available data from participants who were withdrawn from the study will be analysed and listed, and all available planned data will be included in summary tables and figures, unless otherwise specified.

- Missing and anomalous concentration data not due to intercurrent events will be handled according to SOP_314000.

9.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.5.1. Statistical Methodology Specification (Part A)

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma concentration-time profiles).

Ethnosensitivity (Part A)
Endpoint / Variables
• AUC(0-t) • Cmax
Model Specification
• Analysis of variance (ANOVA) will be performed on log-transformed data to determine the point estimate for the comparison of Japanese to Caucasian participants. • This analysis will be repeated for each of the PK parameters at the 450 mg dose level. • The 90% confidence interval for the mean difference of the log-transformed data will be calculated. The equivalent 90% confidence interval for the geometric means will be provided.
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
• Table of: o Geometric means and ratio of geometric means with 90% CI.

9.5.2. Statistical Methodology Specification (Part B)

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma concentration-time profiles).

Note that the intravenous PK data for bioavailability analyses will be taken from the Caucasian stratum in Part A.

Bioavailability (Part B)
Endpoint / Variables
• AUC(0-t)
Model Specification
• Analysis of variance (ANOVA) will be performed on log-transformed data to determine the point estimate for the comparison of SC and IV administration. • The resulting estimated difference is the log point estimate of the absolute bioavailability (Fabs). • This analysis will be conducted at the 450 mg dose level only. • The 90% confidence interval for the mean difference of the log-transformed data will be calculated. The equivalent 90% confidence interval for the geometric means will be provided.
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
• Table of: o Geometric means and ratio of geometric means with 90% CI.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of GSK2831781 administered IV in Japanese and Caucasian healthy volunteers and SC in Caucasian healthy volunteers. The individual participant PK parameters will be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses. Any inter-ethnic differences in the PK will also be investigated.

10.1. Statistical Analyses / Methods

A summary of the planned population pharmacokinetic analyses is outlined below:

- A previous PopPK model developed based on the drug plasma and total serum sLAG3 concentrations collected during the first-time in human study 200630 (GSK Document Number 2017N352860_00) will be fitted to the drug plasma concentration-time data using the nonlinear mixed effects modelling software NONMEM.
- Individual post-hoc estimated PK parameters will be summarised descriptively.
- To support this analysis a PopPK dataset will be generated. The details for the dataset specifications are provided in Appendix 9: Population Pharmacokinetic (PopPK) Analyses.

Detailed PopPK methodology is presented in Appendix 9: Population Pharmacokinetic (PopPK) Analyses.

11. PHARMACODYNAMIC ANALYSES

11.1. Secondary Pharmacodynamic Analyses

11.1.1. Endpoint / Variables

Parameter	Parameter Description
LAG3+	• LAG3$^+$ T cell numbers and frequencies in blood. The following cell populations will be reported: ○ CD4$^+$CD45RA$^-$J11L1$^+$ ○ CD4$^+$CD45RA$^-$REA351$^+$ ○ CD4$^-$CD45RA$^-$J11L1$^+$ ○ CD4$^-$CD45RA$^-$REA351$^+$

11.1.2. Summary Measure

Absolute value and percent change from baseline (%CFB) are of interest.

Part A: Data will be available at baseline and at day 1 (6h, 24h), 4, 8, 15, 29, 43, 57, 85 and 112.

Part B: Data will be available at baseline and at day 2, 4, 8, 15, 29, 43, 57, 85 and 112.

11.1.3. Population of Interest

The secondary pharmacodynamics analyses will be based on the Safety population, unless otherwise specified.

11.1.4. Strategy for Intercurrent (Post-Randomization) Events

A 'While on-study' strategy will be implemented for intercurrent events.

- Withdrawn participants may be replaced in the study. Replacement participants will be dosed with the planned treatment of the withdrawn participant.

- All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 11.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

11.2. Exploratory Pharmacodynamic Analyses

11.2.1. Endpoint / Variables

Parameter	Parameter Description
sLAG3	• Concentration of soluble LAG3 in blood.
Regulatory T cells	• $CD3^{+}CD4^{+}CD45RA^{-}CD25^{+}CD127^{lo}FoxP3^{+}$ Regulatory T cell numbers and frequencies in blood

11.2.2. Summary Measure

Absolute value and percent change from baseline (%CFB) are of interest.

sLAG3:

Part A: Data will be available at baseline and at day 1 (1h, 2h, 6h, 12h, 24h), 3, 4, 8, 15, 22, 29, 43, 57, 71, 85 and 112.

Part B: Data will be available at baseline and at day 2, 3, 4, 6, 8, 11, 15, 18, 22, 29, 43, 57, 71, 85 and 112.

Regulatory T cells:

Part A: Data will be available at baseline and at day 4 and 112.

11.2.3. Population of Interest

The exploratory pharmacodynamics analyses will be based on the Safety population, unless otherwise specified.

11.2.4. Strategy for Intercurrent (Post-Randomization) Events

A 'While on-study' strategy will be implemented for intercurrent events.

- Withdrawn participants may be replaced in the study. Replacement participants will be dosed with the planned treatment of the withdrawn participant.

- All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 11.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of this analysis is to characterize the pharmacokinetic / pharmacodynamic (PK/PD) relationship of GSK2831781 administered IV in Japanese and Caucasian healthy volunteers and SC in Caucasian healthy volunteers. Any inter-ethnic differences in the PK/PD relationship will also be investigated.

12.1. Statistical Analyses / Methods

A summary of the planned population PK/PD analyses are outlined below:

- A previous PopPK/PD model developed based on the individual post hoc predicted PK parameters and all available cell depletion data from the first-time in human study 200630 (GSK Document Number 2017N352860_00) will be fitted to the drug plasma concentration (or PK parameters) and PD data using the nonlinear mixed effects modelling software NONMEM.

- To support this analysis a PK/PD dataset will be generated. The details for the dataset specifications are provided in Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses.
- Detailed PK/PD methodology is presented in Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses.

13. IMMUNOGENICITY ANALYSES

13.1. Endpoint / Variables

Parameter	Parameter Description
ADAs	• Anti-drug antibodies over time.

13.2. Summary Measure

Incidence and duration of anti-drug antibodies (ADA).

The GSK2831781 immunogenicity response will be summarized for the binding antibody assay by treatment group and timepoint. The table will include the number and proportion of participants in each result category for each visit. Binding confirmatory assay results will be categorized as Negative, Positive, or Unknown. Positive samples in the binding assay are further categorized as Transient Positive (i.e. single positive response that does not occur at the final assessment) or Persistent Positive (i.e. positive response that occurs at least 2 consecutive assessments or a single result at the final assessment). Titre for samples confirming positive in the binding assay will be reported in listings.

Parts A and B: Data will be available at baseline and at day 29, 57, 85 and 112.

13.3. Population of Interest

The immunogenicity analyses will be based on the Safety population, unless otherwise specified.

13.4. Strategy for Intercurrent (Post-Randomization) Events

A 'While on-study' strategy will be implemented for intercurrent events.

- Withdrawn participants may be replaced in the study. Replacement participants will be dosed with the planned treatment of the withdrawn participant.

- All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 13.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

14. REFERENCES

GSK Document Number 2018N393275_01. Study ID 207823: A randomised, double-blind, placebo-controlled Phase I study of the safety and tolerability, pharmacokinetics, and pharmacodynamics of a single intravenous dose of GSK2831781 in healthy Japanese and Caucasian participants, and a single subcutaneous dose of GSK2831781 in healthy Caucasian participants. 06-MAY-2019.

GSK Document Number 2017N352860_00. Study ID 200630: A randomised, double blind (sponsor unblinded), placebo controlled, single ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a IV dose of GSK2831781 in healthy volunteers and patients with plaque psoriasis.

15. APPENDICES

15.1. Appendix 1: Protocol Deviation Management

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan. Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset. This dataset will be the basis for the summaries and listings of protocol deviations.

15.2. Appendix 2: Schedule of Activities

15.2.1. Part A: Japanese and Caucasian Participants – IV dose

Procedure	Screening (up to 28 days before Dosing)	Day -1	Day 1 (Hours)							Days 3 – 85										Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0 h[1]	1 h	2 h (end of infusion)	6 h	12 h	24 h	3 2	4 2	8	15	22	29	43	57	71	85	
Window			-60 min		±10 min	+30 min[4]	±30 min	±30 min	±60 min			±1 d	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	±3 d	±7d
Informed Consent	X																			
Inclusion and Exclusion Criteria	X	X																		
Demography	X																			
Full physical examination including height and weight	X																			X
Medical history (includes substance usage)	X																			
Past and Current Medical Conditions	X																			

Procedure	Screening (up to 28 days before Dosing)	Day -1	Day 1 (Hours)							Days 3 – 85										Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0 h[1]	1 h	2 h (end of infusion)	6 h	12 h	24 h	3 [2]	4 [2]	8	15	22	29	43	57	71	85	
Window			-60 min		±10 min	+30 min[4]	±30 min	±30 min	±60 min			±1 d	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	±3 d	±7d
Serology (HIV, HBV, HCV, CMV, EBV, VZV)	X																			
TB screening (QuantiFERON ± PPD)	X																			
Breath Alcohol Screen	X	X																		
Urine Drug Screen	X	X																		
Haematology & Clinical Chemistry	X	X							X	X		X	X		X	X	X		X	X
Urinalysis	X	X							X	X		X	X		X	X	X		X	X
12-Lead ECG[5]	X		X				X		X										X	X
Vital Signs[6]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Screening (up to 28 days before Dosing)	Day -1	Day 1 (Hours)							Days 3 – 85										Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0 h[1]	1 h	2 h (end of infusion)	6 h	12 h	24 h	3 [2]	4 [2]	8	15	22	29	43	57	71	85	
Window			-60 min		±10 min	+30 min[4]	±30 min	±30 min	±60 min			±1 d	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	±3 d	±7d
Randomization		X																		
IMP Administration				<==========																
Resident in unit		<==========																		
Local Tolerability			X			X	X	X	X											
sLAG3 concentrations			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK			X		X	X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity			X												X		X		X	X
LAG3+ Cell Depletion and Immunophenotyping			X				X		X		X	X	X		X	X	X		X	X
Genetic Sample[8]			X																	
AE/ SAE Review	SAEs collected from signing of informed consent form; AEs collected continuously from time of first dose.																			
Concomitant Medication	Monitored from screening until the end of the final treatment period.																			

Procedure	Screening (up to 28 days before Dosing)	Day -1	Day 1 (Hours)							Days 3 – 85										Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0 h[1]	1 h	2 h (end of infusion)	6 h	12 h	24 h	3 [2]	4 [2]	8	15	22	29	43	57	71	85	
Window			-60 min		±10 min	+30 min[4]	±30 min	±30 min	±60 min			±1 d	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	±3 d	±7d
Review																				

Footnotes:

1. All post dose time points are in reference to the start of infusion.
2. Assessments at these visits should be on the scheduled day however can be at any time in the day.
3. Early withdrawal assessments will be the same as Follow-Up.
4. End of infusion assessment time window is +30 minutes for all assessments except for the PK sample which should be collected just before the end of the infusion.
5. ECG in triplicate at screening and single at all other time points.
6. Vital Signs to be taken every 30 minutes from start of infusion until completion of 2hr post dose monitoring period.
7. PK sample at end of infusion should be collected just before the end of the infusion.
8. The genetic sample is optional and can be taken any time after consent has been signed and the participant is randomized.

15.2.2. Part B: Caucasian Participants – SC dose

Procedure	Screening (up to 28 days before Dosing)	Day - 1	Day 1			Days 2-85														Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0h	Post Dose[1]	2[2]	3[2]	4[2]	6[2]	8	11	15	18	22	29	43	57	71	85	
Window			-60 min							±1d	±2d	±2d	±2d	±2d	±2d	±3d	±3d	±3d	±3d	±7d
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		
Demography	X																			
Full physical examination including height and weight	X																			X
Medical history (includes substance usage)	X																			
Past and current medical conditions	X																			
Serology (HIV, HBV, HCV, CMV, EBV, VZV)	X																			
TB screening (QuantiFERON ± PPD)	X																			

Procedure	Screening (up to 28 days before Dosing)	Day - 1	Day 1			Days 2-85														Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0h	Post Dose[1]	2[2]	3[2]	4[2]	6[2]	8	11	15	18	22	29	43	57	71	85	
Window			-60 min							±1d	±2d	±2d	±2d	±2d	±2d	±3d	±3d	±3d	±3d	±7d
Breath Alcohol Screen	X	X																		
Urine Drug Screen	X	X																		
Haematology & Clinical Chemistry	X	X				X	X			X		X			X	X	X		X	X
Urinalysis	X	X				X	X			X		X			X	X	X		X	X
12-Lead ECG[4]	X		X		X[5]	X													X	X
Vital Signs[6]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																		
IMP Administration				X[7]																
Resident in Unit		<==========																		
Local tolerability at injection sites			X		X[8]	X		X		X										
sLAG3 concentrations			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity			X												X		X		X	X

Procedure	Screening (up to 28 days before Dosing)	Day - 1	Day 1			Days 2-85														Follow Up/Early Withdrawal (112 Days post dose)[3]
			Pre-Dose	0h	Post Dose[1]	2[2]	3[2]	4[2]	6[2]	8	11	15	18	22	29	43	57	71	85	
Window			-60 min							±1d	±2d	±2d	±2d	±2d	±2d	±3d	±3d	±3d	±3d	±7d
LAG3+ Cell Depletion			X			X		X		X		X			X	X	X		X	X
Genetic Sample[9]			X																	
AE/SAE Review	SAEs collected from signing of informed consent form; AEs collected continuously from time of first dose.																			
Concomitant medication review	Monitored from screening until the end of the final treatment period.																			

Footnotes:

1. All post dose time points are in reference to the first injection of IMP.
2. Assessments at these visits should be on the scheduled day however can be at any time in the day.
3. Early withdrawal assessments will be the same as Follow-Up.
4. ECG in triplicate at screening and single at all other time points.
5. ECG to be performed 6 hours post dose.
6. Vital Signs to be taken every 30 minutes from first IMP injection until completion of 2hr post dose monitoring period.
7. IMP administration consists of 3 syringes, all 3 syringes are to be administered as closely together as possible (preferably within 10 minutes).
8. Post dose Local tolerability at injection sites to be reviewed at 2, 6, 12, and 24 hours post dose.
9. The genetic sample is optional and can be taken any time after consent has been signed and the participant is randomized.

15.3. Appendix 3: Assessment Windows

15.3.1. Definitions of Assessment Windows for Analyses

No assessment windows will be defined for analyses. Summaries and analyses will be based on nominal visits.

15.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

15.4.1. Study Phases for Parts A and B

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

Study Phase	Definition
Pre-Treatment	Date/Time ≤ Study Treatment Start Date/Time
Treatment Emergent	Date/Time > Study Treatment Start Date/Time

15.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is prior to study treatment.
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

15.4.2. Treatment Emergent Flag for Adverse Events

Adverse Events will be flagged as Treatment Emergent as described in the table in Section 15.4.1, where the AE Start Date/Time will be considered.

15.5. Appendix 5: Data Display Standards & Handling Conventions

15.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	Each of the following directories will be used for both Parts A and B. : \arprod\gsk2831781\mid207823\internal_01 : \arprod\gsk2831781\mid207823\interim_01 : \arprod\gsk2831781\mid207823\final_01
Analysis Datasets	
• Analysis datasets will be created according to Integrated Data Standards Library (IDSL) GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for SAC.	

15.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings.

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits

• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data | Refer to IDSL Statistical Principle 6.06.1
Categorical Data | N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

15.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to PKOne standards. Note: Concentration values will be imputed as per GUI_51487.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created. Dataset specification will be detailed in a separate document.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created. Dataset specification will be detailed in a separate document.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: None
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to SOP_314000.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to PKOne.

15.6. Appendix 6: Derived and Transformed Data

15.6.1. General (Parts A and B)

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit 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.
Study Day

• Calculated as the number of days from Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Dose Date → Study Day = Ref Date – Dose Date
  • Ref Data ≥ Dose Date → Study Day = Ref Date – Dose Date + 1

15.6.2. Study Population

Age
• Only year of birth will be collected on the CRF and birth date will be presented in listings as 'YYYY'. • GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as '30th June' and then calculated based on the dose date.

15.6.3. Safety

ECG Parameters
RR Interval

• If RR interval (msec) is not provided directly, then RR can be derived as:
  ○ If QTcF is machine read, then:
  $$RR - \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$
  ○ If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value, then do not derive.

Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Fridericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcF will be derived as: $$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$
Laboratory parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character

ECG Parameters
value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits → '< x' becomes x – 0.01 o Example 2: 1 Significant Digit → '> x' becomes x + 0.1 o Example 3: 0 Significant Digits → '< x' becomes x – 1

15.7. Appendix 7: Reporting Standards for Missing Data

15.7.1. Premature Withdrawals

Element	Reporting Detail
General	• In both Parts A and B, participant study completion (i.e. as specified in the protocol) is defined as having completed all phases of the study including the last scheduled assessment shown in the SoA (Section 15.2). • Withdrawn participants may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Section 15.3 or will be summarised as withdrawal visits.

15.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated using a "blank" in participant listing displays, unless all data for a specific visit are missing (in which case the data is excluded from the table). ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

15.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• In case of partial dates (i.e. day missing, only month and year present) recorded for AE start and end, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered Treatment Emergent as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the last contact date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date: '01' will be used for the day if the month is not missing, and '01-Jan' will be used if both month and day are missing. ○ If the partial date is a stop date: '28/29/30/31' will be used for the day if the month is not missing, and '31-Dec' will be used if both month and day are missing. ○ For medications recorded in the eCRF as prior medications, the earlier of this imputed date or the day before the treatment start date will be used.

Element	Reporting Detail
	• The recorded partial date will be displayed in listings.

15.8. Appendix 8: Values of Potential Clinical Importance

15.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (> x)**
Haematocrit	Ratio of 1	Male		0.54
		Δ from BL	↓ 0.075	
Haemoglobin	g/L	Male		180
		Δ from BL	↓ 25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Eosinophil Count	$x10^9$/ L			1
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (> x)**
Blood urea nitrogen	mmol/L			10.5
Calcium	mmol/L		2	2.75
Creatinine	μmol/L	Δ from BL		↑ 26
eGFR	ml/min/1.73m^2		60	
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total Protein	g/L		50	85

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

15.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

15.8.3. 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
Temperature	ºC	<35	≥37.5

15.8.4. Urinalysis

Urinalysis			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
Bilirubin		High	>1+
Glucose		High	>1+
Ketone		High	>2+
Leukocytes (dipstick)		High	>1+
Nitrite		High	Positive
Occult blood (dipstick)		High	>1+
pH		Low	<4.6
		High	>8
Protein		High	>1+
RBC (microscopy)	cells/hpf	High	>3
Specific gravity		Low	<1.001
		High	>1.035
Urobilinogen	mg/dL	High	>1
WBC (microscopy)	cells/hpf	High	>5

15.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

15.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

PopPK dataset specification will be provided as a separate document.

15.9.2. Population Pharmacokinetic (PopPK) Methodology

An exploratory graphical analysis of the drug plasma concentration-time data will be performed by generating the plots as presented in Appendix 12: List of Data Displays.

A previous PopPK model developed from the first time in human study 200630 (GSK Document Number 2017N352860_00), incorporating linear and non-linear (target mediated drug disposition (TMDD), Michaelis-Menten) elimination pathways, will be used to fit the drug plasma concentration-time data. The model will be updated accordingly to describe the absorption profiles after SC doses of GSK2831781. For this update it will be assumed that the distribution and elimination of GSK2831781 will be the same regardless of the route of administration (IV or SC).

The appropriateness of the updated model will be assessed by the objective function value (OFV), successful convergence, covariance estimation, shrinkage, parameter uncertainty, standard Goodness-of-Fit (GoF) and simulation-based diagnostic plots e.g. Visual Predictive Check (VPC).

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a VPC is done, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, time of PK sampling and individual values of model covariates, if any). The median and the 10th and 90th will be compared to the observed data. Stratification by dose level and administration route of GSK2831781 or geographic ancestry will be used.

The individual PK parameters will be computed from the PopPK model and will be summarised by treatment group and geographic ancestry.

15.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

15.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

PK/PD dataset specification will be provided as a separate document.

15.10.2. Pharmacokinetic / Pharmacodynamic Methodology

An exploratory graphical analysis of the drug effect on $LAG3^+$ cell depletion, sLAG3 concentrations and regulatory T cells count will be performed by generating the PD plots as presented in Appendix 12: List of Data Displays.

A previous indirect response model developed from all available cell depletion data from the first-time in human study 200630 (GSK Document Number 2017N352860_00) will be fitted to the current PD data using the nonlinear mixed effects modelling software NONMEM. Data relative to $CD4^+CD45RA^-1B4^+$ cell count will be used to model T cell depletion.

The appropriateness of the PopPK/PD model will be assessed by the OFV, successful convergence, covariance estimation, shrinkage, parameter uncertainty, standard GoF and simulation-based diagnostic plots e.g. VPC.

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a VPC is done, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, time of PD sampling and individual values of model covariates, if any). The median and the 10th and 90th will be compared to the observed data. Stratification by dose level and administration route of GSK2831781 or geographic ancestry will be used.

15.11. Appendix 11: Abbreviations & Trade Marks

15.11.1. Abbreviations

Abbreviation	Description
ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransaminase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
AUC(0-t)	Area under the plasma concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
A&R	Analysis and Reporting
BUN	Blood Urea Nitrogen
CI	Confidence Interval
Cmax	Maximum observed plasma concentration
CMV	Cytomegalovirus
CPEM	Clinical Pharmacology and Experimental Medicine
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case Record Form
CSV	Comma-separated values
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DP	Decimal Places
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
F	Bioavailability
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GCDO	Global Clinical & Data Operations
GCSD	Global Clinical Sciences & Delivery
GoF	Goodness-of-Fit
GSK	GlaxoSmithKline
HARP	Harmonized Analysis and Reporting Process
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
INR	International normalized ratio

Abbreviation	Description
IP	Investigational Product
IV	Intravenous
LAG3	Lymphocyte Activation Gene-3
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
NQ	Non-quantifiable
OFV	Objective Function Value
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PKPD	Pharmacokinetic / Pharmacodynamic
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red Blood Cell
RC	(Interim) Review Committee
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
sLAG3	Soluble LAG3
SMG	Safety and Medical Governance
SoA	Schedule of Activities
SOP	Standard Operation Procedure
TA	Therapeutic Area
TB	Tuberculosis
TLF	Tables, Listings & Figures
tmax	Time of occurrence of Cmax
TMDD	Target Mediated Drug Disposition
ULN	Upper limit of normal
VPC	Visual Predictive Check
VZV	Varicella zoster virus
WBC	White Blood Cell
WNL	Windows Non-Linear

15.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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

15.12. Appendix 12: List of Data Displays

15.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.20	-
Safety	2.1 to 2.34	2.1 to 2.2
Pharmacokinetic	3.1 to 3.8	3.1 to 3.4
Population Pharmacokinetic (PopPK)	4.1 to 4.x*	4.1 to 4.x*
Pharmacodynamic	5.1 to 5.7	5.1 to 5.10
Pharmacokinetic / Pharmacodynamic	6.1 to 6.x*	6.1 to 6.x*
Section	**Listings**	
ICH Listings	1 to 66	
Other Listings	67 to x*	

* PopPK and PK/PD displays will be generated by CPMS as needed; the number of displays is not pre-defined.

15.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	-	-	POP_Ln
Safety	SAFE_Fn	-	SAFE_Ln
Pharmacokinetic	-	PK_Tn	-
Population Pharmacokinetic (PopPK)	-	-	-
Pharmacodynamic	PD_Fn	-	PD_Ln
Pharmacokinetic / Pharmacodynamic	-	-	-

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

15.12.3. Deliverables

Delivery	Description
IA	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

15.12.4. Study Population Tables

Part A

Study Population Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Part A: Summary of Subject Disposition for the Subject Conclusion Record	Add footnote: Note: "Subjects" is used to refer to "Participants" in all data displays to reflect GSK display standards. By treatment and geographic ancestry.	IA SAC
1.2.	Screened	ES6	Part A: Summary of Screening Status and Reasons for Screen Failure		SAC
Protocol Deviation					
1.3.	Safety	DV1	Part A: Summary of Important Protocol Deviations	By treatment and geographic ancestry. Include Total column.	SAC
Population Analysed					
1.4.	Screened	SP1	Part A: Summary of Study Populations	By treatment and geographic ancestry.	IA SAC
Demographic and Baseline Characteristics					
1.5.	Safety	DM1	Part A: Summary of Demographic Characteristics	By treatment and geographic ancestry.	IA SAC
1.6.	Safety	DM5	Part A: Summary of Race and Racial Combinations	Only include race detail categories with >0 subjects. By treatment.	SAC
1.7.	Randomized	DM11	Part A: Summary of Age Ranges	By treatment and geographic ancestry.	SAC
Medical Conditions					

Study Population Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	Safety	MH1	Part A: Summary of Past Medical Conditions	By treatment and geographic ancestry.	SAC
1.9.	Safety	MH1	Part A: Summary of Current Medical Conditions	By treatment and geographic ancestry.	SAC
Exposure and Treatment Compliance					
1.10.	Safety	EX1	Part A: Summary of Exposure to Study Treatment	By treatment and geographic ancestry.	SAC

Part B

Study Population Tables (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.11.	Safety	ES1	Part B: Summary of Subject Disposition for the Subject Conclusion Record	By treatment.	SAC
1.12.	Screened	ES6	Part B: Summary of Screening Status and Reasons for Screen Failure		SAC
Protocol Deviation					
1.13.	Safety	DV1	Part B: Summary of Important Protocol Deviations	By treatment. Include Total column.	SAC
Population Analysed					
1.14.	Screened	SP1	Part B: Summary of Study Populations	By treatment.	SAC
Demographic and Baseline Characteristics					
1.15.	Safety	DM1	Part B: Summary of Demographic Characteristics	By treatment.	SAC

Study Population Tables (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.16.	Safety	DM5	Part B: Summary of Race and Racial Combinations	Only include race detail categories with >0 subjects. By treatment.	SAC
1.17.	Randomized	DM11	Part B: Summary of Age Ranges	By treatment.	SAC
Medical Conditions					
1.18.	Safety	MH1	Part B: Summary of Past Medical Conditions	By treatment.	SAC
1.19.	Safety	MH1	Part B: Summary of Current Medical Conditions	By treatment.	SAC
Exposure and Treatment Compliance					
1.20.	Safety	EX1	Part B: Summary of Exposure to Study Treatment	By treatment.	SAC

15.12.5. Safety Tables

Part A

Safety Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	AE1	Part A: Summary of All Adverse Events by System Organ Class and Preferred Term	IA: By geographic ancestry. SAC: By treatment and geographic ancestry.	IA SAC
2.2.	Safety	AE3	Part A: Summary of Drug-Related Adverse Events	IA: By geographic ancestry. SAC: By treatment and geographic ancestry.	IA SAC
2.3.	Safety	AE3	Part A: Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency	By treatment and geographic ancestry.	SAC
2.4.	Safety	AE5A	Part A: Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Page by treatment and geographic ancestry.	SAC
2.5.	Safety	AE5A	Part A: Summary of Drug-Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Page by treatment and geographic ancestry.	SAC
Serious and Other Significant Adverse Events					
2.6.	Safety	AE16	Part A: Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	IA: By geographic ancestry. SAC: By treatment and geographic ancestry.	IA SAC
2.7.	Safety	AE3	Part A: Summary of Serious Drug-Related Adverse Events by Overall Frequency	IA: By geographic ancestry. SAC: By treatment and geographic ancestry.	IA SAC
2.8.	Safety	AE3	Part A: Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	By treatment and geographic ancestry.	SAC

Safety Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
2.9.	Safety	LB1	Part A: Summary of Chemistry Changes from Baseline	By treatment and geographic ancestry.	SAC
Laboratory: Haematology					
2.10.	Safety	LB1	Part A: Summary of Haematology Changes from Baseline	By treatment and geographic ancestry. IA: Only include the following parameters: Neutrophils, Lymphocytes.	IA SAC
Laboratory: Urinalysis					
2.11.	Safety	LB1	Part A: Summary of Urine Concentration Changes from Baseline	By treatment and geographic ancestry.	SAC
Laboratory: Hepatobiliary (Liver)					
2.12.	Safety	LIVER1	Part A: Summary of Liver Monitoring/Stopping Event Reporting	By treatment and geographic ancestry.	IA SAC
2.13.	Safety	LIVER10	Part A: Summary of Hepatobiliary Laboratory Abnormalities	By treatment and geographic ancestry.	SAC
ECG					
2.14.	Safety	EG1	Part A: Summary of ECG Findings	By treatment and geographic ancestry.	SAC
2.15.	Safety	EG10	Part A: Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	By treatment and geographic ancestry.	SAC
2.16.	Safety	EG2	Part A: Summary of Change from Baseline in ECG Values by Visit	By treatment and geographic ancestry.	SAC
Vital Signs					
2.17.	Safety	VS1	Part A: Summary of Change from Baseline in Vital Signs	By treatment and geographic ancestry.	SAC

Part B

Safety Tables (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.18.	Safety	AE1	Part B: Summary of All Adverse Events by System Organ Class and Preferred Term	By treatment.	SAC
2.19.	Safety	AE3	Part B: Summary of Drug-Related Adverse Events	By treatment.	SAC
2.20.	Safety	AE3	Part B: Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency	By treatment.	SAC
2.21.	Safety	AE5A	Part B: Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Page by treatment.	SAC
2.22.	Safety	AE5A	Part B: Summary of Drug-Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Page by treatment.	SAC
Serious and Other Significant Adverse Events					
2.23.	Safety	AE16	Part B: Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	By treatment.	SAC
2.24.	Safety	AE3	Part B: Summary of Serious Drug-Related Adverse Events by Overall Frequency	By treatment.	SAC
2.25.	Safety	AE3	Part B: Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	By treatment.	SAC
Laboratory: Chemistry					
2.26.	Safety	LB1	Part B: Summary of Chemistry Changes from Baseline	By treatment.	SAC
Laboratory: Haematology					
2.27.	Safety	LB1	Part B: Summary of Haematology Changes from Baseline	By treatment.	SAC

Safety Tables (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Urinalysis					
2.28.	Safety	LB1	Part B: Summary of Urine Concentration Changes from Baseline	By treatment.	SAC
Laboratory: Hepatobiliary (Liver)					
2.29.	Safety	LIVER1	Part B: Summary of Liver Monitoring/Stopping Event Reporting	By treatment.	SAC
2.30.	Safety	LIVER10	Part B: Summary of Hepatobiliary Laboratory Abnormalities	By treatment.	SAC
ECG					
2.31.	Safety	EG1	Part B: Summary of ECG Findings	By treatment.	SAC
2.32.	Safety	EG10	Part B: Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	By treatment.	SAC
2.33.	Safety	EG2	Part B: Summary of Change from Baseline in ECG Values by Visit	By treatment.	SAC
Vital Signs					
2.34.	Safety	VS1	Part B: Summary of Change from Baseline in Vital Signs	By treatment.	SAC

15.12.6. Safety Figures

Part A

Pharmacokinetic Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Haematology					
2.1.	Safety	[Non-standard] SAFE_F1	Part A: Individual Plots of Haematology	By treatment and geographic ancestry. Only include the following parameters: Neutrophils, Lymphocytes.	IA
2.2.	Safety	[Non-standard] SAFE_F2	Part A: Mean (±SD) Plots of Haematology	By treatment and geographic ancestry. Only include the following parameters: Neutrophils, Lymphocytes.	IA

15.12.7. Pharmacokinetic Tables

Part A

Pharmacokinetic Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
3.1.	PK	PK01	Part A: Summary of GSK2831781 Plasma Pharmacokinetic Concentration-Time Data	Include 95% Confidence Interval for the mean. By treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC
Pharmacokinetic Parameters					
3.2.	PK	PK03	Part A: Summary of Derived GSK2831781 Plasma Pharmacokinetic Parameters	Include 95% Confidence Interval for the mean. By treatment and geographic ancestry.	IA SAC
3.3.	PK	PK05	Part A: Summary of Log-Transformed Derived GSK2831781 Plasma Pharmacokinetic Parameters	By treatment and geographic ancestry.	IA SAC
Pharmacokinetic Statistical Analyses					
3.4.	PK	[Non-standard] PK_T1	Part A: Table of Ethnosensitivity Model Results		SAC

Part B

Pharmacokinetic Tables (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
3.5.	PK	PK01	Part B: Summary of GSK2831781 Plasma Pharmacokinetic Concentration-Time Data	Include 95% Confidence Interval for the mean. By treatment.	SAC
Pharmacokinetic Parameters					
3.6.	PK	PK03	Part B: Summary of Derived GSK2831781 Plasma Pharmacokinetic Parameters	Include 95% Confidence Interval for the mean. By treatment.	SAC
3.7.	PK	PK05	Part B: Summary of Log-Transformed Derived GSK2831781 Plasma Pharmacokinetic Parameters	By treatment.	SAC
Pharmacokinetic Statistical Analyses					
3.8.	PK	[Non-standard] PK_T1	Part B: Table of Bioavailability Model Results		SAC

15.12.8. Pharmacokinetic Figures

Part A

Pharmacokinetic Figures (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
3.1.	PK	PK24	Part A: Individual GSK2831781 Plasma Concentration-Time Plots (Linear and Semi-log) by Treatment and Geographic Ancestry	By treatment and geographic ancestry. IA: do not show subject IDs. Different colours and symbols for treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC
3.2.	PK	PK19	Part A: Mean (±SD) GSK2831781 Plasma Concentration-Time Plots (Linear and Semi-log) by Treatment and Geographic Ancestry	By treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC

Part B

Pharmacokinetic Figures (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
3.3.	PK	PK24	Part B: Individual GSK2831781 Plasma Concentration-Time Plots (Linear and Semi-log) by Treatment	By treatment.	SAC
3.4.	PK	PK19	Part B: Mean (±SD) GSK2831781 Plasma Concentration-Time Plots (Linear and Semi-log) by Treatment	By treatment.	SAC

15.12.9. Pharmacokinetic Population (PopPK) Tables

Tables will be generated by CPMS as needed for part A & B.

15.12.10. Pharmacokinetic Population (PopPK) Figures

Figures will be generated by CPMS as needed for part A & B.

15.12.11. Pharmacodynamic Tables

Part A

Pharmacodynamic Tables (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LAG3+ T Cells					
5.1.	Safety	PD1	Part A: Summary of LAG3+ T Cells in Blood by Visit	Absolute, %CFB. By treatment and geographic ancestry. By cell populations as defined in 11.1.1. IA: only include data up to Day 29.	IA SAC
Soluble LAG3					
5.2.	Safety	PD1	Part A: Summary of sLAG3 in Blood by Visit	Absolute, %CFB. By treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC
Regulatory T Cells					
5.3.	Safety	PD1	Part A: Summary of Regulatory T Cells in Blood by Visit	Absolute, %CFB. By treatment.	SAC
Immunogenicity					
5.4.	Safety	IMM1	Part A: Summary of Positive Immunogenicity Results		SAC

Part B

Pharmacodynamic Tables (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LAG3+ T Cells					
5.5.	Safety	PD1	Part B: Summary of LAG3+ T Cells in Blood by Visit	Absolute, %CFB. By treatment. By cell populations as defined in 11.1.1.	SAC
Soluble LAG3					
5.6.	Safety	PD1	Part B: Summary of sLAG3 in Blood by Visit	Absolute, %CFB. By treatment.	SAC
Immunogenicity					
5.7.	Safety	IMM1	Part B: Summary of Positive Immunogenicity Results		SAC

15.12.12. Pharmacodynamic Figures

Part A

Pharmacodynamic Figures (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LAG3+ T Cells					
5.1.	Safety	[Non-standard] PD_F1	Part A: Individual Plot of LAG3+ T Cells in Blood Over Time	Absolute, %CFB. By treatment and geographic ancestry. Page by cell population, as defined in 11.1.1. IA: do not show subject IDs. Different colours and symbols for treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC
5.2.	Safety	[Non-standard] PD_F2	Part A: Mean (±SD) Plot of LAG3+ T Cells in Blood Over Time	Absolute, %CFB. By treatment and geographic ancestry. Page by cell population, as defined in 11.1.1. IA: only include data up to Day 29.	IA SAC
Soluble LAG3					
5.3.	Safety	[Non-standard] PD_F1	Part A: Individual Plot of sLAG3 in Blood Over Time	Absolute, %CFB. By treatment and geographic ancestry. IA: do not show subject IDs. Different colours and symbols for treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC
5.4.	Safety	[Non-standard] PD_F2	Part A: Mean (±SD) Plot of sLAG3 in Blood Over Time	Absolute, %CFB. By treatment and geographic ancestry. IA: only include data up to Day 29.	IA SAC

Regulatory T Cells					
5.5.	Safety	[Non-standard] PD_F1	Part A: Individual Plot of Regulatory T Cells in Blood Over Time	Absolute, %CFB. By treatment.	SAC
5.6.	Safety	[Non-standard] PD_F2	Part A: Mean (±SD) Plot of Regulatory T Cells in Blood Over Time	Absolute, %CFB. By treatment.	SAC

Part B

Pharmacodynamic Figures (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LAG3+ T Cells					
5.7.	Safety	[Non-standard] PD_F1	Part B: Individual Plot of LAG3+ T Cells in Blood Over Time	Absolute, %CFB. By treatment. Page by cell population, as defined in 11.1.1.	SAC
5.8.	Safety	[Non-standard] PD_F2	Part B: Mean (±SD) Plot of LAG3+ T Cells in Blood Over Time	Absolute, %CFB. By treatment. Page by cell population, as defined in 11.1.1.	SAC
Soluble LAG3					
5.9.	Safety	[Non-standard] PD_F1	Part B: Individual Plot of sLAG3 in Blood Over Time	Absolute, %CFB. By treatment.	SAC
5.10.	Safety	[Non-standard] PD_F2	Part B: Mean (±SD) Plot of sLAG3 in Blood Over Time	Absolute, %CFB. By treatment.	SAC

15.12.13. Pharmacokinetic / Pharmacodynamic Tables

Tables will be generated by CPMS as needed for part A & B.

15.12.14. Pharmacokinetic / Pharmacodynamic Figures

Figures will be generated by CPMS as needed for part A & B.

15.12.15. ICH Listings

Part A

ICH Listings (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Safety	ES2	Part A: Listing of Reasons for Study Withdrawal		SAC
2.	Screened	ES7	Part A: Listing of Reasons for Screen Failure		SAC
3.	Safety	SD2	Part A: Listing of Reasons for Study Treatment Discontinuation		SAC
4.	Safety	BL1	Part A: Listing of Subjects for Whom the Treatment Blind was Broken		SAC
5.	Safety	TA1	Part A: Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
6.	Safety	DV2	Part A: Listing of Important Protocol Deviations		SAC
7.	Safety	IE3	Part A: Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	Screened	SP3	Part A: Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
9.	Safety	DM2	Part A: Listing of Demographic Characteristics		SAC
10.	Safety	DM9	Part A: Listing of Race		SAC
Medical Conditions and Prior/Concomitant Medications					
11.	Safety	MH2	Part A: Listing of Current/Past Medical Conditions		SAC
12.	Safety	CM2	Part A: Listing of Concomitant Medications		SAC

ICH Listings (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
13.	Safety	EX3	Part A: Listing of Exposure Data		SAC
Adverse Events					
14.	Safety	AE7	Part A: Listing of Subject Numbers for Individual Adverse Events		SAC
15.	Safety	AE8	Part A: Listing of All Adverse Events		IA SAC
16.	Safety	AE2	Part A: Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
17.	Safety	AE8CPA	Part A: Listing of Serious Adverse Events (Fatal & Non-Fatal)	Include fatal and non-fatal status	SAC
18.	Safety	AE8	Part A: Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
19.	Safety	AE8	Part A: Listing of Other Significant Adverse Events		SAC
20.	Safety	AE14	Part A: Listing of Reasons for Considering as a Serious Adverse Event		SAC
Hepatobiliary (Liver)					
21.	Safety	MH2	Part A: Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
22.	Safety	SU2	Part A: Listing of Substance Use for Subjects with Liver Stopping Events		SAC
23.	Safety	LIVER6	Part A: Listing of Liver Stopping Event Information for RUCAM Score		SAC
24.	Safety	LIVER7	Part A: Listing of Liver Biopsy Details		SAC

ICH Listings (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
25.	Safety	LIVER8	Part A: Listing of Liver Imaging Details		SAC
All Laboratory					
26.	Safety	LB5	Part A: Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance		SAC
27.	Safety	LB5	Part A: Listing of Laboratory Values of Potential Clinical Importance		SAC
28.	Safety	LB14	Part A: Listing of Laboratory Data with Character Results	IA: Only include the following parameters: Neutrophils, Lymphocytes	IA SAC
29.	Safety	UR2A	Part A: Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
ECG					
30.	Safety	EG3	Part A: Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
31.	Safety	EG3	Part A: Listing of ECG Values of Potential Clinical Importance		SAC
32.	Safety	EG5	Part A: Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		SAC
Vital Signs					
33.	Safety	VS4	Part A: Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

Part B

ICH Listings (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
34.	Safety	ES2	Part B: Listing of Reasons for Study Withdrawal		SAC
35.	Screened	ES7	Part B: Listing of Reasons for Screen Failure		SAC
36.	Safety	SD2	Part B: Listing of Reasons for Study Treatment Discontinuation		SAC
37.	Safety	BL1	Part B: Listing of Subjects for Whom the Treatment Blind was Broken		SAC
38.	Safety	TA1	Part B: Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
39.	Safety	DV2	Part B: Listing of Important Protocol Deviations		SAC
40.	Safety	IE3	Part B: Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
41.	Screened	SP3	Part B: Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
42.	Safety	DM2	Part B: Listing of Demographic Characteristics		SAC
43.	Safety	DM9	Part B: Listing of Race		SAC
Medical Conditions and Prior/Concomitant Medications					
44.	Safety	MH2	Part B: Listing of Current/Past Medical Conditions		SAC
45.	Safety	CM2	Part B: Listing of Concomitant Medications		SAC
Exposure and Treatment Compliance					
46.	Safety	EX3	Part B: Listing of Exposure Data		SAC

ICH Listings (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
47.	Safety	AE7	Part B: Listing of Subject Numbers for Individual Adverse Events		SAC
48.	Safety	AE8	Part B: Listing of All Adverse Events		SAC
49.	Safety	AE2	Part B: Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
50.	Safety	AE8CPA	Part B: Listing of Serious Adverse Events (Fatal & Non-Fatal)	Include fatal and non-fatal status	SAC
51.	Safety	AE8	Part B: Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
52.	Safety	AE8	Part B: Listing of Other Significant Adverse Events		SAC
53.	Safety	AE14	Part B: Listing of Reasons for Considering as a Serious Adverse Event		SAC
Hepatobiliary (Liver)					
54.	Safety	MH2	Part B: Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
55.	Safety	SU2	Part B: Listing of Substance Use for Subjects with Liver Stopping Events		SAC
56.	Safety	LIVER6	Part B: Listing of Liver Stopping Event Information for RUCAM Score		SAC
57.	Safety	LIVER7	Part B: Listing of Liver Biopsy Details		SAC
58.	Safety	LIVER8	Part B: Listing of Liver Imaging Details		SAC
All Laboratory					
59.	Safety	LB5	Part B: Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance		SAC

ICH Listings (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
60.	Safety	LB5	Part B: Listing of Laboratory Values of Potential Clinical Importance		SAC
61.	Safety	LB14	Part B: Listing of Laboratory Data with Character Results		SAC
62.	Safety	UR2A	Part B: Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
ECG					
63.	Safety	EG3	Part B: Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
64.	Safety	EG3	Part B: Listing of ECG Values of Potential Clinical Importance		SAC
65.	Safety	EG5	Part B: Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		SAC
Vital Signs					
66.	Safety	VS4	Part B: Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

15.12.16. Non-ICH Listings

Part A

Non-ICH Listings (Part A)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
67.	Safety	[Non-standard] POP_L1	Part A: Listing of Dose Dispensation Deviations	By geographic ancestry.	IA
Pharmacokinetic Data					
68.	PK	PK07	Part A: Listing of GSK2831781 Plasma Pharmacokinetic Concentration-Time Data		SAC
69.	PK	PK13	Part A: Listing of Derived GSK2831781 Plasma Pharmacokinetic Parameters		SAC
Pharmacodynamic: LAG3+ T Cells					
70.	Safety	[Non-standard] PD_L1	Part A: Listing of $LAG3^{+}$ T cells in Blood		SAC
Pharmacodynamic: Soluble LAG3					
71.	Safety	[Non-standard] PD_L1	Part A: Listing of sLAG3 in Blood		SAC
Pharmacodynamic: Regulatory T Cells					
72.	Safety	[Non-standard] PD_L1	Part A: Listing of Regulatory T Cells in Blood		SAC
Pharmacodynamic: Immunogenicity					
73.	Safety	IMM2	Part A: Listing of Immunogenicity Results		SAC

Part B

Non-ICH Listings (Part B)					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Local Tolerability					
74.	Safety	[Non-standard] SAFE_L1	Part B: Listing of Injection Sites and Injection Site Reactions		SAC
Pharmacokinetic Data					
75.	PK	PK07	Part B: Listing of GSK2831781 Plasma Pharmacokinetic Concentration-Time Data		SAC
76.	PK	PK13	Part B: Listing of Derived GSK2831781 Plasma Pharmacokinetic Parameters		SAC
Pharmacodynamic: LAG3+ T Cells					
77.	Safety	[Non-standard] PD_L1	Part B: Listing of $LAG3^{+}$ T Cells in Blood		SAC
Pharmacodynamic: Soluble LAG3					
78.	Safety	[Non-standard] PD_L1	Part B: Listing of sLAG3 in Blood		SAC
Pharmacodynamic: Immunogenicity					
79.	Safety	IMM2	Part B: Listing of Immunogenicity Results		SAC

15.13. Appendix 13: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request