TITLE PAGE

Protocol Title: 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.

Protocol Number: 207823/ amendment 01

Compound Number: GSK2831781

Study Phase: Phase 1

Short Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of GSK2831781 after an intravenous dose in healthy Japanese and Caucasian participants, and a subcutaneous dose in healthy Caucasian participants.

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

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SPONSOR SIGNATORY:

PPD

Ramiro Castro-Santamaria MD MPH MBA
VP Clinical Sciences

6 May 2019
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	06-MAY-2019	2018N393275_01
Original Protocol	*13-Mar-2019*	2018N393275_00

Amendment 1 06-MAY-2019

Overall Rationale for the Amendment: This is a protocol amendment with changes to the exclusion criteria, ECG assessment time points, inclusion of medical management guidance, clarification regarding the re-start of dosing and changes to the wording regarding the recording of SAEs. This amendment was made as per MHRA's request for study approval.

Section # and Name	Description of Change *Bolded text indicates newly added text, and strikethrough indicates deleted text.	Brief Rationale
2.2 Schedule of Activities Part B	The SoA was amended to include additional ECG monitoring post-dose on Day 1 and Day 2 of Part B.	This amendment was made so that ECG monitoring in Part B is in line with monitoring in Part A of the study.
6.2 Exclusion Criteria #13	The following change was made: ~~Absolute~~ n**N**eutrophil ~~count <1.5x10^9/L~~ or lymphocyte count**s below the normal range** ~~≤0.8x10^9/L~~.	Participants with any grade of neutropenia are excluded.
6.2 Exclusion Criteria #14	The following change was made: Estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation ~~<60mL~~ **≤90mL**/min/1.73 m^2 at screening.	The value has been amended to ensure a healthy participant population.
7.1 Study Intervention(s) Administered	GSK2831781, [redacted]	The concentration of [redacted] has been amended [redacted], it was previously listed as [redacted] in error.
8.3 Role of Safety Review Team	An amendment was made to include the following: **If the study is halted due to safety concerns based on a decision by the SRT (or DRC; see 11.1.5), and a subsequent decision is made to restart dosing, this will only occur after competent authority authorization via a substantial amendment.**	This amendment was made for clarification surrounding the restarting of dosing during the trial.
9.1.5 Infusion-related Reactions	An amendment was made to include guidance on medical management of infusion-related reactions (section 9.1.5),	This provides guidance if any of the reactions mentioned occur in a participant during the study.

Section # and Name	Description of Change *Bolded text indicates newly added text, and strikethrough indicates deleted text.	Brief Rationale
	hypersensitivity reactions (section 9.1.6) and cytokine-release syndrome (9.1.7).	
9.2.1 Time Period and Frequency for Collecting AE and SAE information	An amendment was made to include the following: Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section. **The exceptions are SAEs, which must be recorded in the CRF AE/SAE section.**	This amendment clarifies the wording as previously it was inconsistent regarding the instructions for SAE recording in the trial.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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.

Short Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of GSK2831781 after an intravenous dose in healthy Japanese and Caucasian participants, and a subcutaneous dose in healthy Caucasian participants.

Rationale: The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity after single intravenous (IV) doses of GSK2831781 administered to healthy Japanese and Caucasian participants, and single subcutaneous (SC) doses administered to healthy Caucasian participants. This information is intended to enable further studies in Japanese participants, and to support defining the optimal SC dose for future studies.

Objectives and Endpoints:

Exploratory endpoints can be found in Section 4, 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 electrocardiogram (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)
• To evaluate the effect of a single IV or SC dose of GSK2831781 on depletion of Lymphocyte Activation Gene-3 (LAG)3^{+} T cells in blood	• PK/PD relationship between plasma PK of GSK2831781 and LAG3^{+} T cells in blood over time

Objectives	Endpoints
• To investigate the immunogenicity of single IV and SC doses of GSK2831781	• Anti-drug antibody (ADAs) over time

Overall 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 single SC doses administered to healthy Caucasian participants.

In Part A, single IV doses of 450 mg GSK2831781 or placebo will be administered to healthy Japanese or Caucasian 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 is planned and will be conducted and reviewed by a Data Review Committee (DRC).

Disclosure Statement:

This is a double-blind, parallel group safety and PK study.

Number of Participants:

Part A: A sufficient number of participants will be randomised such that 8 evaluable Japanese participants (6:2 GSK2831781:Placebo) and 8 evaluable Caucasian participants (6:2 GSK2831781:Placebo) complete Part A, at the same dose level in each stratum. A total of 16 evaluable participants are needed to complete part A, however up to a maximum of 32 participants may be enrolled if a dose reduction is needed.

Part B: A sufficient number of participants will be randomised such that 20 evaluable Caucasian participants (8:8:4 450 mg : 150 mg : placebo) complete Part B. A total of 20 evaluable participants are needed to complete Part B, however up to a maximum of 30 participants may be enrolled if a dose reduction is needed (see Section 7.7).

Evaluable is defined as a participant who has been dosed and has safety and PK data up to Day 29.

Intervention Groups and Duration:

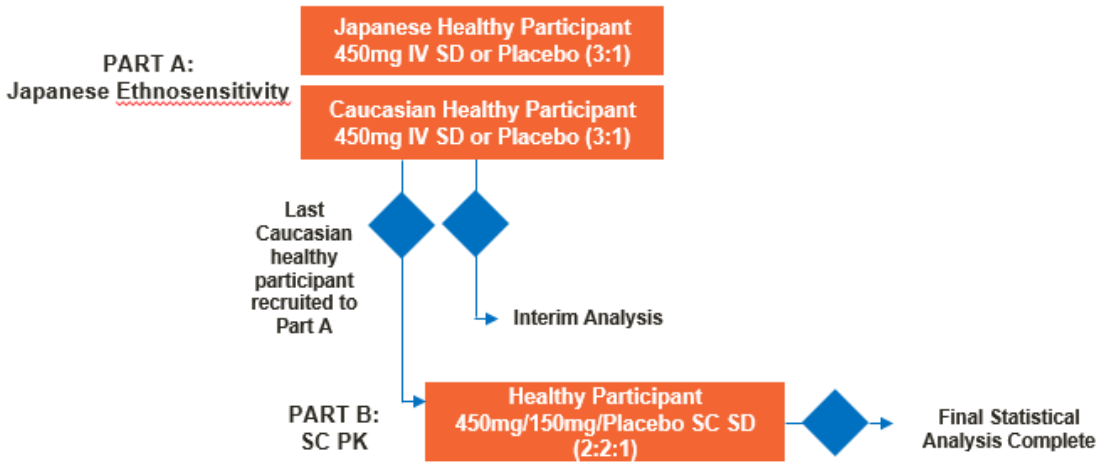
This is a two-part study. Part A is designed to investigate whether there are any differences due to ethnicity in safety and tolerability, or PK and PK/PD relationship in blood between healthy Japanese and Caucasian participants following a single IV 450 mg dose of GSK2831781. Participants will be randomised to GSK2831781 or placebo, with stratification by ethnicity. 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 the Part A will be dosed, unless stopping criteria have been met.

Once the final Caucasian participant has been recruited into Part A of the study, recruitment to Part B may commence. Part B will 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 150 mg GSK2831781, 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 Part B, as this will be the first experience with SC administration in humans, the first two participants dosed will be randomised so that 1 participant will receive 150 mg GSK2831781 and 1 will receive placebo, and injection sites monitored. Since the 450 mg SC dose is delivered as 3x 150 mg injections at discrete injection sites, sentinel dosing at this dose level is not required, as local tolerability will have been assessed at the 150 mg dose level and systemic exposure at 450 mg IV in Part A. After review of sentinel safety data at 46 hours post-dose, the remaining participants in Part B will be dosed, unless stopping criteria have been met.

The study duration, including screening and follow-up, is not expected to exceed 147 days for any participant in the study.

1.2. Schema



2. SCHEDULE OF ACTIVITIES (SOA)

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.

The timing and number of planned study assessments, including safety, pharmacokinetic, and pharmacodynamic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2.2. Part B: Caucasian Participants – Subcutaneous 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.

The timing and number of planned study assessments, including safety, pharmacokinetic, and pharmacodynamic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety.

3. INTRODUCTION

3.1. Study Rationale

GSK2831781 is a humanised, Antibody-Dependent Cell Cytotoxicity (ADCC)-enhanced, depleting monoclonal antibody that is specific to the Lymphocyte Activation Gene-3 (LAG3) protein. LAG3 is a transmembrane receptor, which is upregulated on T cells following activation [Workman, 2002]. Increased expression of LAG3 on T cells has been observed in inflamed tissue in a range of immunoinflammatory diseases, including ulcerative colitis [Slevin, 2018], Crohn's disease and psoriasis, but the number of $LAG3^+$ cells in healthy tissues remains very low. Further, $LAG3^+$ cell depletion in psoriasis showed preliminary evidence of clinical efficacy in a First Time In Humans (FTIH)/Phase 1b trial [Ellis, 2019, and see Section 3.2 Background and GSK2831781 Investigator Brochure (IB)]. However, as only 0.5-5% of T cells in blood and secondary lymphoid organs express LAG3, GSK2831781 should spare $LAG3^-$ resting memory and naïve T cells, as well as the majority of natural regulatory T cells responsible for normal immune homeostasis. By rapid and potent depletion of $LAG3^+$ T cells in diseased tissues, there is the potential to achieve fast and long-lasting disease remission of T cell-driven immunoinflammatory diseases. Additionally, given the highly selective nature of depletion, there may be improved safety and tolerability compared to current standard of care in many of these conditions.

The purpose of this study is to evaluate the safety, tolerability, PK, PD and immunogenicity after single IV doses of GSK2831781 administered to healthy Japanese and Caucasian participants, and single SC doses administered to healthy Caucasian participants. This information is intended to enable further studies in Japanese patients with immunoinflammatory diseases, and to support defining the optimal SC dose for future studies.

3.2. Background

Clinical experience with GSK2831781 to date comes from a single IV ascending dose Phase 1a/1b study (NCT02195349, GSK Study 200630) in healthy participants (up to 0.15 mg/kg) and patients with active mild to moderate plaque psoriasis (0.5 – 5 mg/kg). No safety or tolerability concerns were identified. Proof of mechanism was achieved, with dose-dependent depletion of $LAG3^+$ cells in blood and skin (psoriasis plaques), positive effects on psoriatic skin disease activity markers such as CD3 and pro-inflammatory messenger RNA (mRNA) transcripts, and preliminary evidence of clinical efficacy in ameliorating psoriasis plaques [Ellis, 2019, and GSK2831781 IB].

GSK2831781 is currently being assessed in a Phase 2 trial (GSK Study 204869) of moderate-severe active ulcerative colitis (UC). This trial explores a range of IV doses for induction of remission (CCI [redacted]), and a single CCI [redacted] dose level (CCI [redacted], administered as two injections of CCI [redacted]) in clinical responders for maintenance of remission. Should a robust proof of concept be achieved in this study, efficacy in additional immunoinflammatory diseases may be explored. In order to include Japanese participants into the Phase 2 development programme, safety and tolerability, and PK at the highest dose level (450 mg IV) needs to be confirmed.

In addition, all experience with GSK2831781 to date is with IV administration. Since the PK has been shown to be non-linear due to target-mediated drug disposition, it is possible that GSK2831781 bioavailability after SC administration may be non-linear, resulting in an apparent dose-dependent bioavailability (see Section 5.5). As the Phase 2 study 204869 explores only a SD level, CCI [redacted], the bioavailability needs to be characterised at both ends of the dose range at which SC GSK2831781 might be administered in future studies to inform on the optimal dosing strategy.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2831781 may be found in the IB.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details.	Mitigation Strategy
Investigational Medicinal Product (IMP) [GSK2831781]		
Neutropaenia	**Non-clinical:** In the repeat dose IV and SC studies in monkeys, marked decreases in absolute neutrophils counts were observed in animals given ≥30 mg/kg/week, without clinical sequelae. Neutropenic nadir is observed approximately 4 weeks after start of dosing and is considered to be reversible based on the transient nature of neutropenia observed in the 26-week repeat dose study and the apparent strong adaptive response in the bone marrow of animals in the 4-week study, both in the presence of high systemic GSK2831781 exposure. **Clinical:** No neutropenia, or trends towards reduced neutrophil counts, were observed in the FTIH study (200630) in healthy volunteers or patients with plaque psoriasis, up to a maximum single dose of 5 mg/kg.	Exclusion criteria for low neutrophil counts (<1.5x10^9/L) at baseline. Neutrophil count and adverse events (AE)/serious adverse events (SAEs) related to neutropaenia will be monitored. Haematological stopping criteria. Investigators should manage participants as clinically indicated if neutropaenia is seen.
Infection	**Non-clinical:** No specific studies have been conducted in	Appropriate exclusion criteria for history of e.g. tuberculosis (TB) (screening for latent infection

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk** Refer to GSK2831781 IB for details.	**Mitigation Strategy**
	nonclinical species to investigate the effect of GSK2831781 on response to viral or bacterial infection. In the 26-week study, natural killer cells were lower (down to 0.1X pre-study values) in 4 of the 8 monkeys dosed at 100 mg/kg/week from Day 29, although levels were at or near the overall pre-study and control group values. A significant proportion of newly activated T cells express LAG3, and therefore T cell proliferation upon encounter with an infectious agent may be inhibited by GSK2831781 if exposure is at the same time. However, it has been demonstrated that in healthy participants only a small proportion of central memory T cells express LAG3, so there is low risk of eliminating central memory of anti-infectious immune response against future encounter. **Clinical:** No clinical concerns regarding infections were identified in the FTIH study (200630).	included) or other relevant chronic infectious disease [e.g. Hepatitis B virus (HBV) and Hepatitis C virus (HCV), Human Immunodeficiency Virus (HIV)]. In addition, participants with a recent infection or evidence of significant active infection will be excluded from the study. Participants will not be allowed to receive live vaccines within the 4 weeks prior to Day 1 or during the study until the end of Follow-Up. Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. If indicated, non-live vaccines may be administered based on a treating physician assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness). Investigators will be advised to counsel participants regarding implications for foreign travel, including possible impact on vaccinations and theoretical risks associated with travel to areas of high endemic infection while exposed to GSK2831781. Prior to consenting, participants will be asked to consider whether any impact this might have on their lifestyle would affect their decision to participate in the study.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk** Refer to GSK2831781 IB for details.	**Mitigation Strategy**
		Close monitoring of participants for infections will be continued up to the Follow-Up visit, and supportive therapy (including anti-infectives) provided as clinically indicated.
Infusion reaction/hypersensitivity	**Non-clinical:** No evidence to date. **Clinical:** No infusion reactions or hypersensitivity to GSK2831781 were observed in the FTIH study (200630).	IMP will be administered by clinical staff at clinical sites with appropriate staff training and facilities for the emergency management of hypersensitivity, angioedema and anaphylaxis. Participants will be resident in the clinical unit for 24 hours following start of IMP administration. Exclusion criteria, stopping criteria and appropriate treatment for hypersensitivity reactions.
Local injection site reaction	**Non-clinical:** A dose-related increase in incidence and/or severity of mononuclear cell perivascular infiltration was observed at SC injection sites of monkeys given ≥30 mg/kg/week. Partial recovery in females and full recovery in males at 30 mg/kg/week was observed after 17 weeks off-dose. Not seen with IV administration. **Clinical:** No reactions were observed following IV administration in the FTIH study (200630).	Participants will be resident in the clinical unit for 24 hours following start of IMP administration, and injection sites will be monitored. Any adverse reactions will be managed appropriately and monitored until resolution.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk** Refer to GSK2831781 IB for details.	**Mitigation Strategy**
Immunogenicity	**<u>Non-clinical:</u>** Administration of GSK2831781 to monkeys leads to an ADA response which is more prevalent at lower doses and is associated with a reduction in GSK2831781 systemic exposure. Neutralizing ADA, observed in one animal given 100 mg/kg/week SC in the 26-Week GLP study, correlated with decreased GSK2831781 plasma concentrations and were associated with immune complex mediated clinical pathology changes and increased heart rate, which were transient and of minimal magnitude. Immunogenicity in nonclinical species is not predictive of the potential for immunogenicity in humans **<u>Clinical:</u>** Pre-existing ADAs and post-dosing ADA have been identified in humans. No adverse reactions or alterations in PK associated with immunogenicity were observed in the FTIH study 200630.	Safety and tolerability is being assessed in participants (including clinical chemistry, haematology, AEs, hypersensitivity reactions). Immunogenicity and the impact, if any, on PK and safety parameters will be monitored.
Cytokine release syndrome (CRS)	**<u>Non-clinical:</u>** Hyper-immune activation leading to activation of the innate immune system is only a theoretical	Appropriate monitoring for clinical symptoms associated with cytokine release such as fever, nausea, chills, hypotension, tachycardia,

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk** Refer to GSK2831781 IB for details.	**Mitigation Strategy**
	safety concern, as there is no *in vitro* and *in vivo* evidence of cytokine release associated with LAG3 and the T cell depletion mechanism. GSK2831781 did not induce cytokine release in the human in vitro assay when using a soluble or immobilised format or in the 4-week study in monkeys. As GSK2831781 is expected to induce ADCC, this may lead to cytokine release due to cell lysis. However, a low proportion of T cells express LAG3, therefore the risk of this is expected to be lower than less targeted depleting mAbs. **Clinical:** No CRS was observed in the FTIH study 200630. There were minor transient increases in serum Tumour Necrosis Factor (TNF)-α concentrations between 6-48 hours after dosing at all dose levels, but no dose-response relationship, and the magnitude of these rises was not clinically relevant. There were no meaningful changes to serum Interleukin (IL)-6, IL-8, Interferon (IFN)-γ or Granulocyte-colony stimulating factor (G-CSF).	asthenia, headache, rash, tongue and throat swelling, and dyspnoea, during and for an appropriate period after dosing. Participants will be resident in the clinical unit for 24 hours following start of IMP administration. Participants will be informed in the Informed Consent Form (ICF) to seek prompt medical advice should symptoms indicative of CRS occur, particularly within 72 hours of dosing. Initially, dosing episodes will be separated by a minimum of 22 hours, until at least 3 participants have been dosed in one of the strata. Study site to include facilities and staff training expertise for emergency care/resuscitation.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk** Refer to GSK2831781 IB for details.	**Mitigation Strategy**
Autoimmune-like reactions	**<u>Non-clinical:</u>** A small percentage of regulatory T cells express LAG3. The clinical relevance of this minority subset of T cells in the pathogenesis of autoimmune reactions is unknown. In the 4-week study minimally increased percentages of subpopulations of regulatory T cells were noted on Day 29 at 100 mg/kg/week IV, which was not observed in monkeys administered 100 mg/kg/week SC. No changes in regulatory T cells were observed in the 26-week study. Increases in anti-keyhole limpet hemocyanin (KLH) immunoglobulin (Ig)M and IgG responses, which were not adverse, were noted after each KLH injection (administered during Weeks 16 and 19) in monkeys given 30 or 100 mg/kg/week for 26-weeks compared to responses in control animals, which persisted in the 30 mg/kg/week group at 12-weeks off-dose. Following an off-dose period of 47 and 50 weeks administration of neoantigen tetanus-toxoid (TT) injection to animals previously administered 30 mg/kg/week, resulted anti-TT IgG antibody levels which were similar to control animals.	Exclusion criteria for uncontrolled medical conditions or any background medical history that the investigator (in consultation with the GSK Medical Monitor) considers would put the participant at unacceptable risk. Participants will undergo regular assessment until GSK2831781 has been cleared and $LAG3^+$ cells expected to replete. AEs that could be related to autoimmunity will be monitored. Given the increases in anti-KLH IgM and IgG responses observed in cynomolgus monkeys, there is a theoretical potential for an enhanced response to vaccination, which has not yet been evaluated in clinical studies. The implications of this are not known but are not considered high risk. Investigators will counsel participants regarding the possible impact on vaccination (both of potential reduced responsiveness and enhanced reaction).

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk** Refer to GSK2831781 IB for details.	**Mitigation Strategy**
	Clinical: No autoimmune phenomena were observed in the FTIH study 200630. In patients who received GSK2831781, clinical activity scores for psoriasis (a T cell-mediated disease) tended to improve over the time course of exposure to GSK2831781.	
Reproductive Toxicity	**Non-clinical:** Whereas there are no data for the drug class or mode of action pointing to a known pregnancy hazard, no animal reproduction testing has been conducted. Therefore, there is the potential for unidentified risks to the embryo-foetus or pregnancy. Doses up to 100 mg/kg/week for 26-weeks did not result in pathology in the reproductive organs of mature monkeys or effects on spermatogenesis staging. **Clinical:** The IMP level of monoclonal antibody (mAb) in human semen is expected to be too low to be of concern.	The study will recruit only male participants. There are no specific contraception requirements for males participating in this study.

3.3.2. Benefit Assessment

There will be no direct benefit to the healthy participants in this study. However, information obtained in this study will inform the conduct of future clinical studies to contribute to the process of developing new therapies for diseases where there is unmet medical need, including UC.

3.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures to minimise risks, the potential risks of participation in this study of GSK2831781 are considered justified and adequately mitigated.

4. 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)
• 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	• GSK2831781 PK concentrations over time following single SC dose

Objectives	Endpoints
SC dose in healthy Caucasian participants (Part B)	
• 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

5. STUDY DESIGN

5.1. Overall 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 10.5 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.

If, following a Safety Review Team (SRT) review, it is felt that the dose level in Part A has to be lowered from 450 mg (see Section 7.7) then the randomisation to the new dose level will also be 6:2 (GSK2831781:Placebo) within both the Japanese and Caucasian strata.

5.2. Number of Participants

Part A: A sufficient number of participants will be randomised such that 8 evaluable Japanese participants (6:2 GSK2831781:Placebo) and 8 evaluable Caucasian participants (6:2 GSK2831781:Placebo) complete Part A, at the same dose level in each stratum. A total of 16 evaluable participants are needed to complete part A, however up to a maximum of 32 participants may be enrolled if a dose reduction is needed (see Section 7.7).

Part B: A sufficient number of participants will be randomised such that 20 evaluable Caucasian participants (8:8:4 450 mg : 150 mg : placebo) complete Part B. A total of 20 evaluable participants are needed to complete Part B, however up to a maximum of 30 participants may be enrolled if a dose reduction is needed (see Section 7.7).

Evaluable is defined as a participant who has been dosed and has safety and PK data up to Day 29.

5.3. Intervention Groups and Duration

5.3.1. Part A

This is a two-part study. Part A 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. Participants will be randomised to GSK2831781 or placebo, with stratification by ethnicity.

The study duration, including screening and follow-up, is not expected to exceed 147 days for any participant in the study.

5.3.2. Part B

Once the final Caucasian participant is recruited into Part A of the study, recruitment to Part B may commence. Part B will 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.

The study duration, including screening and follow-up, is not expected to exceed 147 days for any participant in the study.

5.4. Participant and Study Completion

A participant is considered to have completed the study if he has completed all phases of the study including the last scheduled assessment shown in the SoA (Section 2).

The participants who withdraw from the study early should be encouraged to complete all visits as set out in the SoA (Section 2); however, if this is not possible at a minimum participants will be encouraged to complete an Early Withdrawal visit, as well as the Follow-Up visit approximately 16 weeks after the dose (Section 8.4) to ensure participant monitoring until drug wash out is achieved.

end of the study is defined as the date of the last visit of the last participant in the study.

5.5. Scientific Rationale for Study Design

5.5.1. Part A (Japanese ethnosensitivity)

IV administration of GSK2831781 at the same dose to both healthy Japanese and Caucasian participants will allow for assessing the ethnic sensitivity of GSK2831781 in terms of safety and tolerability, PK and PD. The dose level for Part A is chosen such that the full PK/PD curve (i.e., from no depletion to full depletion, then to repletion) and the maximum exposure following a SD used in subsequent Phase 2 and potential Phase 3 studies will be achieved (see Section 5.7). Single (rather than repeat) doses are required so that the repletion of $LAG3^+$ cells in blood can be quantified. This study will be performed in healthy participants to ensure full pharmacological characterisation of GSK2831781 without confounding from disease-specific factors or other medications.

Doses of approximately 450 mg IV (5 mg/kg dose level) were administered to patients with psoriasis in the FTIH study (200630) and repeat IV doses of CCI are approved for administration to patients with ulcerative colitis in the Phase 2 study (204869). In Study 200630, there was no imbalance in AEs between participants receiving GSK2831781 or placebo, the 5 mg/kg dose was well-tolerated, and target pharmacology in blood had been saturated by doses of 0.5 mg/kg and above. Healthy participants were included in the FTIH study up to a dose level of 0.15 mg/kg IV; but thereafter GSK2831781 was administered to patients with active plaque psoriasis to inform on safety at higher doses and provide pharmacodynamic and clinical readouts in a population with active T cell-driven inflammation.

In Study 200630, there were no observed differences in PK between healthy volunteers and psoriasis patients, nor a dose-response in relation to safety parameters. However, since this study will be the first experience of the 450 mg dose in healthy participants, to bridge from the FTIH, dosing episodes will initially be separated by a minimum of 22 hours (in addition to the 2-hour period of IV dose administration). This will ensure that, at the start of the study, only one participant is dosed in a 24-hour period. Once three participants in one of the strata have been dosed (meaning that at least one participant has received active drug), there will be a further 46-hour observation period (on top of the 2-hour dose administration interval). If no events meeting study stopping criteria have occurred (see Section 8), the remaining participants in Part A can then be dosed.

5.5.2. Part B (subcutaneous PK)

By including cohorts with SC administration in the same study, the bioavailability (and PK in general) of GSK2831781 by the SC route can be assessed. The FTIH study (200630) demonstrated that PK in healthy volunteers was not linear, with evidence of target-mediated drug disposition (TMDD), much of which was mediated by sLAG3. The regulation and source of sLAG3 is currently uncertain. TMDD due to sLAG3 was saturated following IV doses of GSK2831781 of 0.5 mg/kg and above, but since the absorption rate of drug from SC tissue will be slower than the infusion rate following an IV dose, it is possible that the impact of this mechanism will have a non-linear effect on SC bioavailability. Characterisation of 150 mg and 450 mg SC doses in the current study, alongside data from the CCI dose in study 204869, will determine whether the

bioavailability is non-linear at these doses via this route, and is necessary to fully inform the dosing strategy for later phase clinical development.

As this will be the first experience with SC administration in humans, sentinel dosing will be used. The first two participants dosed will be randomised so that 1 participant will receive 150 mg GSK2831781 and 1 will receive placebo, and injection sites monitored. Since the 450 mg SC dose is delivered as 3x 150 mg injections at discrete injection sites, sentinel dosing at this dose level is not required, as local tolerability will have been assessed at the 150 mg dose level and systemic exposure at 450 mg IV in Part A. After review of sentinel safety data at 46 hours post-dose, the remaining participants in Part B will be dosed, unless stopping criteria have been met (see Section 8).

5.6. Placebo control

This study includes placebo arms to allow for a valid evaluation of AEs attributable to treatment versus those independent of treatment.

5.7. Justification for Dose

To date, GSK2831781 has been administered as single IV doses to healthy volunteers (0.0003-0.15 mg/kg) and patients with mild-moderate plaque psoriasis (0.5-5 mg/kg) in the FTIH study 200630. In the highest dose cohort in study 200630, the average administered dose was 472 mg. No imbalance in adverse effects attributed to GSK2831781 was seen between participants receiving active treatment versus placebo in any of the cohorts, AEs were generally mild in nature and severity, and overall GSK2831781 was well-tolerated and safety considered acceptable.

At the highest dose studied in study 200630 (5 mg/kg, or on average 472 mg), near complete depletion of $LAG3^+$ T cells in blood was achieved, with these T cells beginning to replenish by approximately Day 42, and in the majority of participants were approximately back to baseline by Day 85. Therefore, it is expected that a dose of 450 mg IV is appropriate to investigate the complete PK/PD relationship. In addition, CCI IV is the highest dose that is tested in the global Phase 2 study (204869) in UC, and so will provide the maximum exposure for evaluation of safety in Japanese participants prior to their inclusion in study 204869.

GSK2831781 exhibits non-linear PK through TMDD. In theory this could result in non-linearity in bioavailability, and therefore two SC doses (150 mg and 450 mg) will be investigated in this study. These doses, in combination with the CCI dose being assessed for maintenance in study 204869, cover the anticipated therapeutic dose range for later phase development.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

TYPE OF PARTICIPANT
1. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and 12-lead ECGs. A participant with a clinical abnormality or laboratory parameter(s) outside the reference range for the population being studied that is not specifically listed in the inclusion or exclusion criteria may be included if the Investigator (in consultation with the GSK Medical Monitor if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or interpretation.
AGE
2. Between 18 and 65 years of age inclusive, at the time of signing the informed consent.

WEIGHT
3. Body weight ≥40 kg and body mass index (BMI) ≤30 kg/m^2.

SEX
4. Male.

INFORMED CONSENT
5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

GEOGRAPHIC ANCESTRY
6. Japanese ancestry, defined as having been born in Japan, being descendants of four ethnic Japanese grandparents and two ethnic Japanese parents, holding a Japanese passport or identity papers, and being able to speak Japanese. Participants should have lived outside Japan for less than 10 years at the time of screening. Caucasian ancestry, defined as Caucasian descent as evidenced by appearance and verbal confirmation of familial heritage (a participant has 2 Caucasian parents and 4 Caucasian grandparents).

6.2. Exclusion Criteria

MEDICAL CONDITIONS
1. History or presence of a disease that in the opinion of the investigator constitutes a risk when taking the study intervention or interfering with study assessment or interpretation of the data. 2. A medical history of severe allergic reaction, angioedema, anaphylaxis, clinically significant drug hypersensitivity reaction, or autoimmune or immunodeficiency disorder. 3. An active infection or a history of serious infections as follows: a. Use of antimicrobials (antibacterials, antivirals, antifungals or antiparasitic agents) for an infection within 30 days before first dose. Topical treatments may be allowed at the Medical Monitor's discretion. b. A history of opportunistic infections. c. Recurrent or chronic infection, or other active infection, that in the opinion of the Investigator might cause this study to be detrimental to the participant. d. Symptomatic herpes zoster within 3 months prior to screening. e. History of TB (active or latent) irrespective of treatment status. f. A positive diagnostic TB test at screening (defined as a positive QuantiFERON test). In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once and if their second test is negative they will be eligible. In the event a second test is also indeterminate, the investigator has the option to undertake PPD testing. If the PPD reaction is <5 mm at 48 to 72 hours, then the participant is eligible. If the reaction is ≥5 mm, or PPD testing is not undertaken, the participant is not eligible. 4. Any planned major surgical procedure during the study. 5. A history of malignant neoplasm within the last 10 years, except for fully treated non-metastatic basal or squamous cell cancers of the skin (within 3 years) that shows no evidence of recurrence.

PRIOR/CONCOMITANT THERAPY
6. Use of prescription or non-prescription drugs (including recreational drugs and herbal medications) within 7 days or 5 half-lives (whichever is longer) prior to dosing, unless in the opinion of the investigator (in consultation with the GSK Medical Monitor), the medication will not interfere with the study or compromise participant safety. Paracetamol (acetaminophen) at doses of ≤4 grams/day, and occasional use of non-steroidal anti-inflammatory drugs (NSAIDs) at licensed doses, are permitted. 7. Received live vaccination within 4 weeks of Day 1, or plan to receive a live vaccination during the study until follow-up. 8. Previous exposure to GSK2831781, or hypersensitivity to any excipients in the clinical formulation of GSK2831781 (see Section 9.1.5). 9. Treatment with biologic agents (such as monoclonal antibodies) within 3 months or 5

half-lives (whichever is longer) prior to dosing.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
10. Participation in a clinical trial and has received an IMP within the following time period prior to screening in the current study: 3 months, 5 half-lives, or twice the duration of the biological effect of the IMP (whichever is longer). 11. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 12. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months.

DIAGNOSTIC ASSESSMENTS*
13. Neutrophil or lymphocyte counts below the normal range. 14. Estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation ≤90 mL/min/1.73 m^2 at screening. 15. Alanine transaminase (ALT) >2x upper limit of normal (ULN) and bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening. 16. Other clinically significant abnormalities of laboratory assessments, as judged by the Investigator and/or GSK Medical Monitor, that could affect the safety of the participant, or the interpretation of the data from the study. 17. Presence of hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb), or positive hepatitis C antibody result at screening (NB. Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained). 18. Positive serology for HIV at screening. 19. Positive pre-study drug/alcohol screen. 20. QTc >450 msec, based on the mean of triplicate ECGs. The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; preferred method), or another method, machine or overread.**

*Retesting in the case of potentially spurious results or sample handling errors is allowed during the screening period.

**Same correction to be used throughout the study.

OTHER EXCLUSIONS
21. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >21 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
22. Unstable lifestyle factors, to the extent that in the opinion of the investigator they would interfere with the ability of a participant to complete the study.

6.3. Lifestyle Considerations

6.3.1. Alcohol Restrictions

Participants will abstain from alcohol for 24 hours prior to each visit to the clinical unit. Additionally, they should refrain from alcohol for 7 days after dosing. Thereafter an average weekly intake of <21 units alcohol is permitted.

6.3.2. Activity

Participants will abstain from strenuous exercise for 48 hours before each visit.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number.

Individuals who pass screening but are not dosed for reasons other than screen failure may be rescreened and should be assigned a new participant number.

Screening assessments that yield aberrant results (e.g., safety laboratory samples) may be repeated once within the screening window by the investigator based upon clinical judgement. Retested participants should be assigned the same participant number as for the initial screening.

7. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Study Intervention(s) Administered

Intervention Name	GSK2831781	Placebo
Type	Biologic	N/A
Dose Formulation	GSK2831781, [redacted]	Commercial saline solution, 0.9% (w/v)
Unit Dose Strength(s)	150 mg/mL	N/A
Dosage Level(s)	IV: 450 mg SC: 150 mg or 450 mg	N/A
Route(s) of Administration	IV infusion or SC injection	IV infusion or SC injection
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor or designee	Supplied by site
Packaging and Labelling	Study intervention will be provided in vial. Each vial will be labelled as required per country requirement.	N/A
[Current/Former Name(s) or Alias(es)]	aLAG3, anti-LAG3	N/A

GSK2831781 is a fully humanized monoclonal antibody and all formulation ingredients have been previously used in the clinic.

Intravenous GSK2831781 (or placebo) will be diluted in 0.9% saline as described in the Study Reference Manual (SRM), and administered over a 2 hour infusion, with active post-dose monitoring for a further 2 hours. Participants will remain resident for a minimum of 24 following IMP administration.

SC GSK2831781 is administered as multiples of 150 mg injections, each provided as 1 mL of GSK2831781 150 mg/mL. Participants randomised to the different dose levels will receive:

- 450 mg dose level: 3x 150 mg GSK2831781.
- 150 mg dose level: 1x 150 mg GSK2831781 and 2x 1 mL 0.9% (w/v) saline for injection.
- Placebo: 3x 1 mL 0.9% (w/v) saline for injection.

Each participant in Part B will therefore receive 3 injections at the dosing visit. In an individual participant, injections should preferably be administered into the same part of the body (arms, legs or abdomen, either on the left or right side or both), but should be separated by a minimum of 2 cm. Syringes will be labelled in a blinded fashion, and the location of each injection will be recorded, so that the locations of active and placebo injections at 150 mg dose level are traceable. This is relevant for assessment of those

participants who receive both active and placebo injections.

7.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.3. Method of Treatment Assignment

At Screening a unique Participant Number (case report form [CRF] number) will be assigned to any participant who has at least one Screening procedure performed, other than informed consent. The unique Participant Number will be used to identify individual participants during the study.

Participants who meet the screening eligibility criteria will be randomised to a treatment group through the IWRS. The IWRS will confirm the participant's CRF number (Participant number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Biostatistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other participant in the study.

Therefore, the randomisation is centrally controlled by the IWRS.

Part A: 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 B: 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
B	150 mg GSK2831781 SC
C	450 mg GSK2831781 SC
Q	Placebo SC

7.4. Blinding

This will be a double-blind study with respect to allocation of GSK2831781 or placebo to participants. All study staff and participants will be blinded with the exception of unblinded pharmacists or delegates.

The following will apply:

- The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind.
- The date and reason for the unblinding must be fully documented in the CRF.
- A participant may continue in the study if the participant's treatment code is unblinded by the investigator or treating physician. If the participant discontinues the date and primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Safety and Medical Governance (SMG) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

Members of the DRC may be unblinded if individual data needs to be reviewed as part of the interim analysis.

7.5. Study Intervention Compliance

- GSK2831781 will be intravenously administered in Part A, and subcutaneously administered in Part B to participants at the site. Administration will be documented in the source documents and reported in the CRF.
- Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

7.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Participants will be questioned about concomitant medication at each study visit.

Paracetamol (acetaminophen) at doses of ≤4 grams/day, and occasional NSAIDs at licensed doses, are permitted for use.

Otherwise, participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Live vaccination is prohibited within 4 weeks of Day 1 until after the Follow-Up visit.

7.7. Dose Modification

Study stopping criteria are detailed in Section 8.2. In addition, if moderate or severe AEs not meeting stopping criteria are consistently observed across participants in a cohort or strata, or if unacceptable pharmacological effects reasonably attributable to GSK2831781 are observed, this will result in review by the SRT prior to additional participants being dosed. This protocol allows for dose reduction if necessary following SRT review (see Section 8.3).

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Intervention

This is a SD study. In rare instances, a participant in Part A may not be able to complete the IV infusion, or a participant in Part B may not receive all 3 injections. In such circumstances, if the study intervention is permanently discontinued, the participant will be encouraged to remain in the study for the planned duration, or minimally to complete safety and PK assessments up to Day 29.

8.2. Study Stopping Criteria

8.2.1. Serious Adverse Events

If one or more participants experience an SAE in either Part A or Part B of the study that can be reasonably attributed to GSK2831781, and which is not a subcutaneous injection site reaction, no further participants will be dosed until a full safety review has taken place and the study will be temporarily halted.

If one or more participants in Part B experience an SAE due to a SC injection site reaction, no further participants will be dosed in Part B until a full safety review has taken place, although dosing in Part A may continue.

Relevant reporting and discussion with the GSK2831781 Safety Review Team (SRT; see Section 8.3 for additional details), relevant GSK personnel, and with the Ethics Committee and Regulatory Agency will then take place. If, following the safety review, a decision is made to restart dosing (which may be at either the same dose or a lower dose), this will only occur after approval of a substantial amendment.

8.2.2. AEs of Special Interest

The following events of note across both Part A and Part B will result in review by the SRT before further participants are dosed:

- A severe opportunistic or atypical infection.
- Cytokine release syndrome of Common Terminology Criteria for Adverse Events (CTCAE) (Version 5) Grade ≥2.
- Serum sickness of CTCAE (Version 5) Grade ≥2.
- A neutrophil count $<0.5 \times 10^9$/L on any occasion (confirmed on repeat testing within 3-5 days), an absolute neutrophil count $<1.0 \times 10^9$/L for 2 weeks, or CTCAE Grade 3 febrile neutropaenia (neutrophil count $<1.0 \times 10^9$/L and fever ≥38.5ºC).

8.2.3. Liver Chemistry Criteria

Liver chemistry study stopping criteria, and individual participant increased monitoring criteria, have been designed to assure participant safety and evaluate liver event aetiology.

- Liver events meeting SAE criteria will be managed as detailed in Section 11.5.

- Liver events characterized by an ALT ≥3x ULN but not meeting SAE criteria, if reasonably attributable to GSK2831781, will result in review by the SRT before further participants are dosed and additional assessments as detailed in Section 11.5.

8.2.4. QTc Criteria

QTc study stopping criteria, and individual participant increased monitoring criteria, have been designed to assure participant safety. The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. Use of Fridericia's formula (QTcF) is preferred in this study. The formula may not be changed or substituted once the participant has been enrolled; for example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well. Safety ECGs and other non-protocol specified ECGs are an exception.

If a participant meets any of the criteria below, this will result in review by the SRT before further participants are dosed, as well as additional monitoring of the affected individual:

- QTc >500 msec.
- Uncorrected QT >600 msec.
- Change from baseline of QTc >60 msec.

With the exception of screening, the QTc should be based on single ECG reading. If an ECG demonstrates a prolonged QTc interval, then a further two ECG readings should be obtained over a brief recording period and the averaged QTc interval used to determine whether the participant meets the criteria to trigger SRT review and for individual further monitoring. Further monitoring will consist at minimum of triplicate ECGs one week later, and then follow-up until values are no longer clinically significant.

8.3. Role of the Safety Review Team (SRT)

An SRT will oversee the safety of participants in this study. The SRT will review blinded safety data at planned interims during the study, and unscheduled as required. Further details of the SRT are described in Section 11.1.5 and the SRT charter.

Unscheduled SRT reviews may be triggered as described in Section 8.2, if moderate or severe AEs are consistently observed across participants in a cohort or strata, or if unacceptable pharmacological effects reasonably attributable to GSK2831781 are observed. Should an unscheduled SRT review of this study be required, possible outcomes may include:

- Restart dosing at the current dose levels.
- Restart dosing but reduce the dose levels in Part A and/or Part B as guided by emerging safety data and data on GSK2831781 plasma concentrations.
- Stop dosing in the relevant part of the study (A or B) but continue with the other part.
- Stop dosing both Part A and Part B.

If the study is halted due to safety concerns based on a decision by the SRT (or DRC; see 11.1.5), and a subsequent decision is made to restart dosing, this will only occur after competent authority authorization via a substantial amendment.

8.4. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities (SoA). See Section 2 Schedule of Activities (SoA) SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.5. Lost to Follow-Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 11.1.9.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns will be managed by the investigator with discussions with the GSK Medical Monitor as required to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Include the maximum amount of blood collected from each participant over the duration of the study and if any repeat or unscheduled samples may be taken, as appropriate.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL over 3 months.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The actual date and time of each blood sample collection will be recorded. The collection, sample handling, processing, storage and shipping procedures are provided in the SRM or equivalent.
- Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.1.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal, Endocrine and Neurological systems. Height and weight will also be measured and recorded at screening.

9.1.2. Vital Signs

Vital signs (to be taken before blood collection for laboratory tests) will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

Blood pressure and pulse measurements will be with a completely automated device. Manual techniques will be used only if an automated device is not available. Temperature measurements should be oral or tympanic.

9.1.3. Electrocardiograms

- Triplicate (at screening) or single 12-lead ECG will be obtained in a semi-supine position, after 5 minutes rest, as outlined in Section 2 (SoA) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study, and this formula may not be changed or substituted once the participant has been screened.
- Where single ECG measurements are obtained, if the QTc measurement fulfils a QTc withdrawal criterion an additional two QTc readings will be obtained and the average of these three measurements will be used. Refer to Section 8.2.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- Where triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

9.1.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 16 weeks after dosing should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.

9.1.5. Infusion-related Reactions

Symptoms and signs of an infusion reaction include tenderness, warmth, redness at the site of injection or along the vein, and/or itching. More severe reactions may additionally include pain at the site of injection, blistering or skin damage.

Management consists of discontinuing the infusion (if possible), hot or cold compresses, and analgesia. A plastic surgery consult should be requested if there is significant skin injury or symptomatic extravasation.

9.1.6. Hypersensitivity Reactions

As GSK2831781 is a fully humanized monoclonal antibody, it is considered unlikely that acute allergic reactions will occur in response to exposure; however, all participants should be monitored carefully for evidence of allergic response.

Participants should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, vomiting, or other symptoms that may represent a hypersensitivity reaction to study intervention. It is important to recognize early signs of a hypersensitivity reaction and prevent progression to a severe reaction. In the case of a mild reaction during dosing, study intervention administration may be reinitiated (with appropriate pre-medication) at the discretion of the investigator.

In the event of a suspected severe acute hypersensitivity reaction or anaphylaxis, sites should manage this in accordance with relevant local or national guidelines (for example, the Resuscitation Council (UK) Emergency Treatment of Anaphylactic Reactions Guidelines for Healthcare Providers (2008). In particular sites should:

- Discontinue administration of study intervention (if still ongoing), and not delay initial treatment due to indefinite diagnosis.
- Ensure adrenaline, chlorphenamine, hydrocortisone, and a resuscitation trolley are immediately available.
- Assess the participant using the **A**irway, **B**reathing, **C**irculation, **D**isability, **E**xposure approach. In the event of a cardiac arrest, initiate cardiopulmonary resuscitation.
- Provide adrenaline as per relevant local/national guidelines if there is any compromise of the participant's airway, breathing or circulation:
- Provide high concentration oxygen via a non-rebreathe mask; fluid resuscitation; initiate ECG monitoring and pulse oximetry; and monitor blood pressure.
- Administer an appropriate antihistamine (e.g., chlorphenamine maleate 10 mg by slow intravenous injection, or intramuscularly).
- Administer hydrocortisone 200 mg by slow intravenous injection, or intramuscularly.
- Acquire two blood samples should be taken for serum tryptase analysis:
    - As soon as possible after the onset of symptoms, and
    - Within 1-2 hours (but no later than 4 hours) from the onset of symptoms.

- Discuss the clinical situation with the relevant hospital medical and/or intensive care team, and arrange transfer to hospital for further treatment and observation as indicated.

9.1.7. Cytokine Release Syndrome

Symptoms and signs of severe Cytokine Release Syndrome (CRS) may include severe headache, muscle pain, nausea, vomiting, diarrhoea, pyrexia, generalised erythema, peripheral vasoconstriction, hypotension, tachycardia and/or tachypnoea.

If CRS is suspected, in addition to assessment for infection, sites should:

- Start high flow oxygen, obtain intravenous access, and start fluid resuscitation.
- Give 100 mg intravenous hydrocortisone, and consider higher doses if the participant is severely unwell.
- Discuss the clinical situation with the relevant hospital medical and/or intensive care team, and arrange transfer to hospital as indicated.
- Take blood for measurement of cytokine levels (including interleukin [IL]-6, IL-8, interferon [IFN]-γ and tumour necrosis factor [TNF]-α), and C-reactive protein (CRP). These should also be measured approximately every other day until symptoms show improvement or an alternative diagnosis is confirmed.
- Treat myalgia with analgesia, and give a suitable intravenous antiemetic (e.g. ondansetron), if required.

9.1.8. Immunosuppression and Infections

Participants with signs and symptoms suggestive of infection should be treated as clinically indicated according to medical best practice. Blood, sputum, urine, and/or stool cultures will be obtained as appropriate for detection and diagnosis of infection. Blood samples for determination of viral serology ± measurement of viral load [cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV)], as well as measurement of immunoglobulins, will be taken if the participant demonstrates clinical symptoms consistent with viral reactivation; serology samples for these viruses will also be tested at screening.

9.1.9. Autoimmunity

There are a small percentage of regulatory T cells that are $LAG3^{+}$ [Gagliani, 2013; Camisaschi, 2010], and therefore investigators should be alert for the development of autoimmunity. Any participant who reports symptoms suspicious for autoimmunity should be investigated and managed as clinically appropriate.

9.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the GSK2831781 (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from consenting participants until the Follow-Up visit at the time point specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g. study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the Follow-Up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section. The exceptions are SAEs, which must be recorded in the CRF AE/SAE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

9.2.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as

defined in Section 8.5). Further information on follow-up procedures is given in Appendix 3.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.3. Treatment of Overdose

For this study, any dose of GSK2831781 greater than the agreed dose level will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

If an overdose is identified by unblinded staff, but is less than 450 mg, this should be documented by the unblinded monitor (including the quantity of the overdosing), but no additional action need be taken.

If the total dose administered has exceeded 450 mg, investigators should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for at least 4 weeks from the date the overdose occurred, and thereafter as advised by the Medical Monitor.
3. Document the quantity of the excess dose.

9.4. Pharmacokinetics

Blood (3 mL per time point) will be collected into K2-ethylenediaminetetraacetic acid (EDTA) tubes and processed to obtain plasma for PK analysis of GSK2831781 at the time points indicated in Section 2, SoA Tables. The actual date and time (24-hour clock time) of each blood sample collection will be recorded.

Details of blood sample collection, processing, storage and shipping procedures are provided in the SRM.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.4.1. Soluble LAG3 (sLAG3)

Venous blood samples will be collected for measurement of sLAG3 as specified in the Section 2, SoA.

9.5. Pharmacodynamics

The PD effect of GSK2831781 on $LAG3^+$ target engagement and cell depletion will be determined through analysis of blood. Blood PD analysis will be undertaken through flow cytometry as specified in the Section 2 SoA.

More detailed immunophenotyping, including identification of regulatory T cells, may be carried out on samples from a subset of participants.

9.6. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 4, Section 11.4 for Information regarding genetic research.

9.7. Immunogenicity Assessments

Antibodies to GSK2831781 will be evaluated in serum samples collected from all participants according to Section 2, SoA. The detection and characterization of antibodies to GSK2831781 will be performed using a validated assay method by or under the supervision of the Sponsor.

Serum samples will be assessed for the presence of ADA using a tiered approach. Samples will first be screened for antibodies binding to GSK2831781. Samples with screening result above the screening cut point will be further assayed in an assay to confirm the specificity of the ADA. Samples testing positive in the confirmation assay will be further assayed through sequential dilution in order to report a titre value. The titre is the reciprocal of the last dilution at which the sample tests positive in the screening assay. Additional analysis may be performed on samples collected to monitor immunogenicity to assess the presence of neutralizing antibodies to GSK2831781 and/or to further characterize the immunogenicity of GSK2831781.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

The primary objective is to determine the safety and tolerability of single IV doses of GSK2831781 in healthy Japanese and Caucasian participants (Part A); or of single SC doses of GSK2831781 in healthy Caucasian participants (Part B). There are no formal hypotheses planned.

10.2. Sample Size Determination

10.2.1. Part A

There will be a minimum of 8 Japanese and 8 Caucasian participants in Part A. The participants in each ethnicity stratum will be randomised 6:2 to GSK2831781 (450 mg) or placebo.

If 0/6 of a particular safety event is observed among the GSK2831781 participants of an ethnicity stratum, then the upper limit of the exact 95% Confidence Interval indicates that a true incidence rate of 41.0% could not be ruled out. Using a Bayesian approach to determine the credible interval around an observed safety event, we will assume a flat Beta (1,1) prior. If in an ethnicity stratum we were to observe 1 safety event out of the 6 participants who received GSK2831781, then the posterior distribution would be Beta (2,6). In that case there is a 95% certainty that the true probability of the safety event lies between 0.04 and 0.58.

The following between-subject coefficients of variation (CV_b) for the geometric means of PK parameters were observed in the FTIH study 200630 following GSK2831781 IV administration:

Study 200630	Treatment group	CV_b (%)	
Volunteer type		AUC (0-t)	Cmax
Healthy volunteer	0.0075 mg/kg	32.0	19.1
Healthy volunteer	0.04 mg/kg	27.3	25.6
Healthy volunteer	0.15 mg/kg	36.8	18.3
Psoriasis patient	0.5 mg/kg	34.2	23.5
Psoriasis patient	1.5 mg/kg	13.8	15.5
Psoriasis patient	5 mg/kg	24.2	22.2

The 5 mg/kg dose corresponds to an average of 472 mg; therefore, the corresponding CV_b %'s are a good approximation for 450 mg.

Assuming a sample size of 6, it is estimated that the lower and upper bounds of the 90% confidence interval for the geometric means of area under the curve (AUC) and Cmax will be within approximately 21.7% and 19.8% of the point estimate respectively.

10.2.2. Part B

There will be a minimum of 20 participants in Part B, randomised 8:8:4 to low dose GSK2831781 (150 mg) or high dose GSK2831781 (450 mg) or placebo.

If 0/8 of a particular safety event is observed among the GSK2831781 participants, then the upper limit of the exact 95% Confidence Interval indicates that a true incidence rate of 33.6% could not be ruled out. Using a Bayesian approach to determine the credible interval around an observed safety event, we will assume a flat Beta (1,1) prior. If on GSK2831781 we were to observe 1 safety event out of the 8 participants, then the posterior distribution would be Beta (2,8). In that case there is a 95% certainty that the true probability of the safety event lies between 0.03 and 0.48.

To date we do not have any GSK2831781 SC PK variability data available. Therefore, literature data was used to obtain informative priors for the absorption rate constant (ka) and bioavailability (F). Using these priors, and the PK/PD relationship derived from the data of the First Time in Humans Study 200630, a sample size of 8 participants on active treatment has a probability of 65% to result in a median cell depletion in blood greater than 90% at week 4 after dosing.

10.2.3. Sample Size Sensitivity

A sample size sensitivity analysis was conducted to investigate different safety event rates. A Bayesian approach was used, specifying a flat Beta (1,1) prior. If the number of subjects who complete each active dose reduce, then the 95% credible interval of the true event rate would change:

N Dosed	Number of a particular safety event observed with GSK2831781	95% certain that the true probability of the safety event lies between
8	2	(0.07, 0.60)
	3	(0.14, 0.70)
7	0	(0.00, 0.37)
	1	(0.03, 0.53)
	2	(0.09, 0.65)
6	2	(0.10, 0.71)
	3	(0.18, 0.82)
5	0	(0.00, 0.46)
	1	(0.04, 0.64)
	2	(0.12, 0.78)
4	0	(0.01, 0.52)
	1	(0.05, 0.72)
	2	(0.15, 0.85)

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who are randomised into the study and receive a randomisation number.
Safety	All randomized participants who receive at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received.
Pharmacokinetic	All safety participants for whom a PK sample was obtained and analysed.

10.4. Statistical Analyses

The final analysis will be performed once all participants in Part A and in Part B have completed their Day 112 visit.

10.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	The primary safety analyses will be based on the “Safety” population. These endpoints will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library standards.

10.4.2. Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Secondary	The PK analyses will be based on the “Pharmacokinetic” population. Plasma GSK2831781 concentration-time data will be analysed by non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: Cmax, tmax, AUC(0-t). Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters. In addition, for log e-transformed variables geometric mean, 95% confidence interval

Endpoint	Statistical Analysis Methods
	and %CVb will be provided. **Ethnicity comparison (Part A):** Analysis of variance (ANOVA) will be performed to determine the point estimate for the comparison of Japanese to Caucasian participants for each of the PK parameters AUC(0-t) and Cmax at each dose level studied, with the 90% confidence interval based on the geometric least square mean of Japanese:Caucasian participants. **Bioavailability Analyses (Part B):** Comparative plots will be provided showing individual values by treatment for each of the PK parameters AUC(0-t) and Cmax. Plots will also be provided showing the adjusted geometric mean ratio of test to reference treatment for AUC(0-t) and Cmax together with 90% confidence intervals. ANOVA will be performed as appropriate to determine the point estimate for absolute bioavailability, Fabs, with 90% confidence interval based on the geometric least square mean of test/reference ratio. The primary statistical analysis will be analysis of variance of loge-transformed AUC(0-t). Fabs is defined as follows: $Fabs = \frac{AUC(0-t)_{subcutaneous}}{AUC(0-t)_{intravenous}}$

10.4.3. Pharmacokinetic/Pharmacodynamic Analysis

Endpoint	Statistical Analysis Methods
Secondary	A population PK/PD analysis will be performed based on the safety population. This will investigate PK, sLAG3 and cell depletion data. In Part A, this analysis may include ethnicity as a covariate.

10.4.4. Other Analyses

For Parts A and B, the immunogenicity assessment will include the incidence (confirmed positive results only) and titres of anti-GSK2831781 binding antibodies at each time point and at any time point post baseline.

Further details of the statistical analyses will be provided in the Reporting Analysis Plan (RAP).

10.5. 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 strataum have complete 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). To aid this decision, an additional interim analysis may also be conducted once all Part A participants complete Day 112. An appropriate committee will conduct the interim analysis, where details will be outlined clearly in the RAP.

A DRC will be utilised in this study to review the interim analyses data. The DRC will be comprised of a predefined subset of study team members. No study personnel with direct contact with sites or site staff will be involved in the DRC (see Appendix 1, Section 11.1.5).

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH (International Conference of Harmonization) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

11.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3. Informed Consent Process

- The investigator or his representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.

11.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Committees Structure

Safety Review Team (SRT)

In line with routine pharmacovigilance, an internal GSK SRT, which will include a limited number of 207823 study team members, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct. The SRT charter outlines the roles and responsibilities in more detail.

Data Review Committee (DRC)

During an Interim Analysis unblinded study data may be reviewed by the DRC, and decisions made based on the outlined criteria included in the DRC charter. 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. No members of the study team involved in the direct day-to-day conduct of the study or in the acquisition of data will take part in the DRC.

11.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.8. Source Documents

- Data reported on the CRF or entered in the electronic case report form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Source Document Agreement.

11.1.9. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

11.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

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 (SGPT)	Total Protein
	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	• 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. 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.

11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
o Results in death
o Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment

in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

11.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes

available.

- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IMP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the Study Reference Manual.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

11.4. Appendix 4: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK2831781 and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to GSK2831781. Genetic research may consist of the analysis of one or more candidate genes, or the analysis of genetic markers throughout the genome, DNA samples will be analysed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK2831781 or study interventions of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2831781 continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

11.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥3x ULN
If ALT ≥3x ULN AND bilirubin[1,2] ≥2x ULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3x ULN AND bilirubin ≥2x ULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT ≥3x ULN AND bilirubin <2x ULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis, as soon as possible, and at least within 7 days after last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin ≥2x ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including paracetamol (acetaminophen), herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT ≥3x ULN AND bilirubin ≥2x ULN or</td></tr>
</table>

Liver Chemistry Stopping Criteria	
within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that subject if ALT ≥3x ULN and bilirubin ≥2x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3x ULN and bilirubin ≥2x ULN (>35% direct bilirubin) or ALT ≥3x ULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HbsAg and HbcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. Instructions for sample handling and shipping are in the SRM.

11.6. Appendix 6: Abbreviations and Trademarks

ABBREVIATIONS

ADA	Anti-drug antibody
ADCC	Antibody-Dependent Cell Cytotoxicity
AE	Adverse event(s)
ALT	Alanine aminotransaminase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
AUC	Area under the curve
AUC(0-t)	Area under the plasma concentration-time curve
BUN	Blood Urea Nitrogen
DRC	Data Review Committee
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
CD3	Cluster of Differentiation
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Cmax	Maximum observed plasma concentration
CMV	Cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-reactive protein
CPK	Creatine phosphokinase

CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV_b	Coefficients of variation
DRC	Data Review Committee
EDTA	Ethylenediaminetetraacetic acid
F	Bioavailability
FTIH	First Time In Human
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator('s) Brochure
ICH	International Council of Harmonization
IEC	Independent Ethics Committees
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IMP	Investigational Medicinal Product

INF	Interferon
INR	International normalized ratio
IRB	Institutional Review Boards
IV	Intravenous
KLH	Keyhole Limpet Hemocyanin
LAG3	Lymphocyte Activation Gene-3
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
mRNA	Messenger ribonucleic acid
MSDS	Material Safety Data Sheet
NIMP	Non-investigational medicinal product
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PPD	Purified protein derivative
QTcF	Corrected QT interval (Fridericia's formula)
RAP	Reporting Analysis Plan
RBC	Red Blood Cell
SAE	Serious adverse event(s)
SC	Subcutaneous
SD	Single dose
SGOT	Serum Glutamic-Oxaloacetic Transaminase

SGPT	Serum Glutamic-Pyruvic Transaminase
sLAG3	Soluble LAG3
SMG	Safety and Medical Governance
SoA	Schedule of Activities
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
tmax	Time of occurrence of Cmax
TMDD	Target-mediated drug disposition
TNF	Tumour Necrosis Factor
TT	Tetanus-toxoid
UC	Ulcerative Colitis
ULN	Upper limit of normal
VZV	Varicella zoster virus
WBC	White Blood Cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

11.7. Appendix 7 : Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

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