TITLE PAGE

Protocol Title: A phase 1, randomised, double-blind, placebo-controlled study of the safety, tolerability, pharmacokinetics and pharmacodynamics of single subcutaneous doses of GSK2330811 in healthy Japanese participants.

Protocol Number: 208564

Compound Number or Name: GSK2330811

Study Phase: Phase 1

Short Title: Safety, tolerability, pharmacokinetics, pharmacodynamics of GSK2330811 after a subcutaneous dose in healthy Japanese participants.

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

Regulatory Agency Identifying Number(s):

EudraCT: 2019-003042-33

Approval Date: 11-SEP-2019

SPONSOR SIGNATORY:

PPD

Sept 11th 2019

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Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A phase 1, randomised, double-blind, placebo-controlled study of the safety, tolerability, pharmacokinetics and pharmacodynamics of single subcutaneous doses of GSK2330811 in healthy Japanese participants.

Short Title: Safety, tolerability, pharmacokinetics, pharmacodynamics of GSK2330811 after a subcutaneous dose in healthy Japanese participants.

Rationale:

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity after single subcutaneous (SC) doses of GSK2330811 administered to healthy Japanese participants. This information is intended to enable future efficacy studies in Japanese patients with relevant diseases, and to support defining the optimal SC dose for future studies in this population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
• To evaluate the safety and tolerability of a single SC dose of GSK2330811 in healthy Japanese participants	• Number of participants reporting adverse events (AEs). • Number of participants reporting serious adverse events (SAEs). • Number of participants with vital signs (blood pressure, heart rate, body temperature) reaching a threshold of potential clinical importance. • Number of participants with treatment emergent abnormal electrocardiogram (ECG) findings. • Number of participants with Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or higher safety laboratory results (clinical chemistry, haematology values where CTCAE grading applies). • Number of participants with treatment emergent abnormal urinalysis findings
Secondary	Secondary

Objectives	Endpoints
• To evaluate the pharmacokinetic (PK) profile of a single SC dose of GSK2330811 in healthy Japanese participants	• Pharmacokinetic parameters (Cmax, AUC, CL/F, Tmax, $t_{1/2}$, Vss/F)
• To assess the potential for anti-drug antibody (ADA) formation following a single SC dose of GSK2330811 in healthy Japanese participants	• Number of participants with anti-GSK2330811 antibodies
• To assess effects of GSK2330811 on platelets and haemoglobin in healthy Japanese participants	• Platelet nadir • Time to platelet nadir • Haemoglobin nadir • Time to haemoglobin nadir

Overall Design:

This is a randomised, double-blind (sponsor-open), placebo-controlled, single-centre study with single SC doses of GSK2330811 administered to healthy male Japanese participants.

- Participants will attend a screening visit at the clinical unit within 30 days of Study Day 1. If eligible for the study, participants will return on Day -1 for overnight admission to the unit.
- Participants will be randomized to either GSK2330811 or placebo in an approximate ratio of 7:3.
- Approximately 10 eligible participants will be admitted to the clinical unit on the day prior to dosing (Day-1). On Day 1, each participant will receive a single SC dose of GSK2330811 or placebo, administered as three separate SC injections. Participants will then remain as an in-patient until discharged on Day 2 after assessments have been performed.
- Participants will then return to the clinical unit for outpatient visits as per the Schedule of Activities (SoA).
- The final follow up visit will be at the clinical unit on Day 126.
- The maximum dose will not exceed 450 mg SC.

Disclosure Statement:

This is a 2-arm, double-blind, parallel group, safety and PK study.

Number of Participants:

Approximately ten participants will be enrolled and dosed (7 GSK2330811: 3 Placebo) with a view to ensuring 8 are evaluable (6 GSK2330811: 2 Placebo).

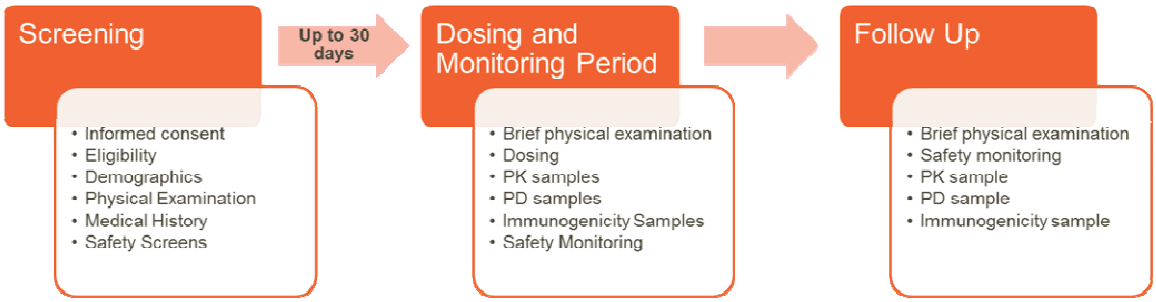
Up to a maximum of 14 participants may be enrolled and dosed.

Intervention Groups and Duration:

This study will include a single cohort of approximately 10 participants randomised to a single dose of 450mg SC GSK2330811 or placebo in a 7:3 ratio (active: placebo).

The study duration, including screening and follow-up, is not expected to exceed 163 days for any participant in the study.

1.2. Schema



1.3. Schedule of Activities (SoA)

Screening Period

Screening Procedure	Screening (up to 30 days prior to Day 1)
Informed Consent	X
Inclusion and Exclusion Criteria	X
Demography	X
Full Physical Exam (incl. weight and height)	X
Medical History and current medical conditions[1]	X
Concomitant Medication Review	X
12 lead ECG in triplicate	X
Vitals (blood pressure, heart rate, body temperature)[2]	X
Breath Alcohol Screen	X
Urine Drug Screen	X
Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV) and Hepatitis C virus (HCV) Screen	X
Tuberculosis (TB) Screening QuantiFERON	X
Haematology/Clinical Chemistry/Urinalysis/Clotting	X
SAE Review	X

1. To include substance usage, family history of premature cardiovascular disease, medication, drug/alcohol history
2. Vital signs are to be taken before blood collection for laboratory tests.

Treatment and Follow-Up Period

Procedure	**Day-1**	**Day 1**					**Day 2**	**Day 3**	**Day 5**	**Day 7**	**Day 10**	**Day 14**	**Day 21**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 126 (follow-up visit)/Early Withdrawal**
											+/- 1 day	**+/- 1 day**	**+/- 1 day**	**+/- 1 day**	**+/- 2 days**	**+/- 2 days**	**+/- 7 days**	**+/- 7 days**
Admission	X																	
In-patient Stay	X	X																
Discharge							X											
Outpatient Visit								X	X	X	X	X	X	X	X	X	X	X
Inclusion and Exclusion Criteria	X																	
Breath Alcohol Screen	X																	
Urine Drug Screen	X																	
		Pre-dose	**0h**	**1h**	**4h**	**8h**	**24h**											
Dosing[3]			X															
Injection Site Reaction Assessment		X[5]	X[5]		X[5]		X[5]											X[5]
Brief Physical Exam	X						X[1]											
Full Physical Exam[6]																		X
Haematology/Clinical Chemistry	X	X[2]					X[1]	X	X	X	X	X	X[2]	X	X	X	X	X
Urinalysis	X									X			X				X	X
12 lead ECG (triplicate)		X								X			X				X	X
Vitals (blood pressure, heart rate, body temperature)[4]	X	X		X[1]	X[1]	X[1]	X[1]	X	X	X	X	X	X	X	X	X	X	X
PK Sampling		X				X[1]	X[1]	X	X	X	X	X	X	X	X	X	X	X
Free & Total OSM Sampling		X				X[1]	X[1]	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Sampling		X										X		X				X
TPO Sampling		X							X		X		X				X	
EPO Sampling		X								X		X	X			X		

Procedure	**Day-1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 7**	**Day 10**	**Day 14**	**Day 21**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 126 (follow-up visit)/Early Withdrawal**
Concomitant Medication Review		Monitored from screening until end of follow-up visit												
SAE/AE Review		SAEs collected from signing of consent form, AEs collected continuously from time of dose												

AE= adverse event; ECG= Electrocardiogram; EPO= Erythropoietin; TPO = Thrombopoietin; OSM= Oncostatin M; PK= pharmacokinetic; SAE= serious adverse event

Footnotes:

1. All post dose time points are in reference to the first injection of IMP.
2. Day 1 Pre-dose sample and Day 21 sample will be fasted for approximately 12 hr and will include lipids
3. IMP administration consists of 3 syringes, all 3 syringes are to be administered as closely together in time as possible
4. Vital signs are to be taken before blood collection for laboratory tests.
5. Assessments should be conducted immediately before first injection (pre-dose) and immediately after last injection (0h). Post dose assessments (4h and 24h) to be conducted in reference to the last injection of IMP. Any injection site reactions to be captured through AE reporting.
6. Full physical exam at follow-up will not include height

- The timing and number of planned study 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. INTRODUCTION

GSK2330811 is a first in class, humanised IgG1 monoclonal antibody that binds and inhibits the action of Oncostatin M (OSM) and is being developed for the treatment of Crohn's disease (CD) and Systemic sclerosis (SSc).

The current strength of the liquid formulation is 150 mg/mL and is presented as a pre-filled syringe (PFS) assembled in a safety syringe device for SC administration.

2.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity after single SC doses of 450 mg GSK2330811 administered to healthy Japanese participants. This information is intended to enable future efficacy studies in Japanese patients with relevant diseases, and to support defining the optimal SC dose for future studies in this population.

2.2. Background

GSK2330811 is a humanised monoclonal antibody that binds and neutralises OSM and is being developed for the treatment of SSc and CD.

OSM is a member of the IL-6 family of cytokines, which is produced by a variety of immune cells including macrophages, activated T-cells and neutrophils in response to infection and tissue injury. OSM signalling on a variety of cell types, including fibroblasts, epithelial, endothelial, smooth muscle cells and hematopoietic cells, drives inflammation, fibrosis and vasculopathy [Hermanns, 2015; Ayaub, 2017].

The safety profile of GSK2330811 has been evaluated in repeat-dose SC 13 and 26-week monkey toxicity studies. The key findings were of a reduction in red cell parameters in the peripheral blood and bone marrow with evidence of a regenerative reticulocyte response and of a transient reduction in platelet counts which showed partial to complete recovery by week 13. In the 13-week toxicity study, the no observed adverse effect level (NOAEL) was considered to be 300 mg/kg/week (the highest dose tested). In the 26-week toxicity study, because of the magnitude of the pharmacology related effects on red blood cell parameters noted the NOAEL was not identified. Of note, for non-pharmacology related findings the NOAEL is considered to be 300 mg/kg/week (highest dose tested). Detailed information can be found in the Investigator's Brochure (IB) for GSK2330811 [GlaxoSmithKline Document Number 2016N284919_02, 2019].

The safety, tolerability and PK of GSK2330811 has been evaluated in a Phase 1 single-dose escalation study in healthy volunteers (201246, NCT02386436, [Reid, 2018]). Thirty participants were exposed to GSK2330811 at doses ranging from 0.1 mg/kg to 6.0 mg/kg. GSK2330811 was well-tolerated, with no serious adverse events (SAEs) reported. The pharmacokinetic profile of GSK2330811 was consistent with that of an IgG1 monoclonal antibody against a soluble cytokine and high levels of target engagement were observed. A reversible reduction in platelet count was observed at dose levels of 1

mg/kg and above, and a low-grade reduction in haemoglobin and red cell count was observed at the highest dose level (6 mg/kg). Both these effects are consistent with the inhibition of the known pharmacology of OSM by GSK2330811. Detailed information can be found in the IB for GSK2330811 [GlaxoSmithKline Document Number 2016N284919_02, 2019].

A repeat dose, proof of mechanism study (201247, NCT03041025) with GSK2330811 in participants with SSc is ongoing, dosing up to 300 mg every two weeks for 6 doses.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2330811 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK2330811		
Thrombocytopaenia	• OSM has been shown to modulate haematopoiesis through an effect on bone marrow stromal cells, haematopoietic progenitors and bone marrow microenvironment [Wallace, 1995; Miyajima, 2000; Tanaka, 2003]. • In the 13 and 26 week repeat dose monkey toxicology studies transient reduction in platelet counts were observed which showed partial to complete recovery by week 13. In the 13 week repeat dose study, platelet counts were comparable to vehicle control monkeys following clearance of GSK2330811 (at the end of an 18 week off drug period). Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019]. • A First Time in Human (FTIH) study of single doses of GSK2330811 in healthy participants demonstrated a dose-dependent, reversible reduction in platelet count at doses between 1 mg/kg and 6 mg/kg. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019].	• Only participants with platelet count ≥LLN will be included in the study. • Participants with any history of known bleeding or coagulation disorders will be excluded. • The use of anti-platelet medications, other than occasional use of non-steroidal anti-inflammatory drugs (NSAIDs), will not be permitted. • Platelet count will be tested at each scheduled visit, until the end of the follow-up period, to ensure careful monitoring. • Haematological Study Stopping criteria and Individual participant enhanced monitoring criteria will be implemented.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Anaemia	• OSM has been shown to modulate haematopoiesis through an effect on bone marrow stromal cells, haematopoietic progenitors and bone marrow microenvironment [Wallace, 1995; Miyajima, 2000; Tanaka, 2003]. • In the 13 and 26 week repeat dose monkey toxicology study progressive decreases in red cell parameters and bone marrow myeloid to erythroid ratios with a compensatory increase in reticulocyte count were noted correlates. In the 13 week repeat dose study there was partial to complete recovery of red cell parameters and reticulocytes following clearance of GSK2330811 (at the end of an 18 week off drug period). Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019]. • A FTIH study of single doses of GSK2330811 in healthy participants showed a reduction in haemoglobin / red cell count at 6 mg/kg. A reticulocytosis was evident from Day 21 in participants receiving 3 mg/kg and 6 mg/kg. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019].	• Only participants with haemoglobin ≥LLN will be included in the study. • Participants with any history of known bleeding or coagulation disorders will be excluded. • Participants will not receive anti-coagulant medications during the study. • Haemoglobin will be tested at each scheduled visit, until the end of the follow-up period, to ensure careful monitoring. • Haematological Study Stopping criteria and Individual participant enhanced monitoring criteria will be implemented.
Infection including reactivation of Mycobacterium tuberculosis	• OSM contributes to immunity in synergy with other cytokines such as TNF and IL-1 which may protect against infection. Therefore, the possibility of an increase in the frequency and/or severity of infection following dosing of GSK2330811 cannot be excluded. • In the 26-week cynomolgus monkey toxicology study decreases in neutrophils (associated with left shift) and eosinophils were noted. Also observed were increases in total lymphocyte count, which was attributed to increased T helper and T cytotoxic cell numbers. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019]. • No dose-related fall in white cell count or leukocyte subsets was observed in the FTIH single ascending dose study of GSK2330811. No excess of infection adverse events was observed in participants receiving GSK2330811. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019].	• Participants will be screened for HIV, HBV, HCV and TB and excluded if positive. • Participants with prior opportunistic or recurrent infection, or evidence of recent or ongoing infection, will be excluded; refer Section 5.2 for details. • Participants planning travel to regions of high endemic infection during the study will be excluded. • Participants will be monitored closely for infection, through regular review of symptoms, signs and laboratory tests during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Vaccination	• Since an immunosuppressive effect of GSK2330811 cannot be excluded, there is a theoretical possibility that GSK2330811 could decrease an individual's immune response to vaccines administered while on therapy • In the monkey 6 month repeat dose study, the antibody response to Keyhole Limpet Hemocyanin (KLH) immunization (anti KLH IgM and IgG) was assessed. Although a delay in the antibody response following primary KLH immunisation was noted, these data are not considered indicative of an inability to mount a T cell dependent B cell response since an antibody response was observed. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019].	• Participants will not be allowed to receive live vaccines within the 4 weeks prior to Day 1, until the end of follow-up. • Investigators should consider the benefit-risk of administering any non-live vaccines during the study.
Hypersensitivity	• Monoclonal antibodies can be associated with systemic hypersensitivity reactions, including angioedema, hypotension and anaphylaxis. • There were no hypersensitivity reactions noted in the FTIH study with GSK2330811.	• Participants with a history of hypersensitivity / allergy that may put them at increased risk of a hypersensitivity reaction will be excluded; refer Section 5.2 (eligibility) for details. • GSK2330811 will be administered by trained clinical staff and participants will be appropriately monitored after dosing in a setting with the capacity to manage any immediate hypersensitivity reactions. • Participants will be educated on the potential for hypersensitivity reactions and the appropriate emergency care.
Immunogenicity	• Biopharmaceutical products may elicit anti-drug antibodies (ADA), which have the potential to modulate PK, PD and/ or produce adverse reactions. • There were no treatment-related anti-GSK2330811 antibodies detected in the FTIH study with GSK2330811.The risk of developing ADA and their clinical consequences are mitigated given that GSK2330811 is a humanized monoclonal antibody against a soluble target	• Serum samples will be collected for detection of ADA at timepoints aligned with regulatory guidelines [EMA, 2017;FDA, 2019].

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatotoxicity	• A potential risk of hepatotoxicity is inferred from studies in OSMRβ knockout mice showing impaired hepatocyte proliferation and tissue remodelling with impaired liver regeneration after liver injury [Nakamura, 2004]. Administration of OSM ameliorated liver injury in wild-type mice. • However, in the 13- and 26-week toxicity studies in healthy cynomolgus monkeys, treatment with GSK2330811 was not associated with any observed liver effects. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019] • Mild, isolated, transient elevations in Alanine aminotransaminase (ALT), Aspartate Aminotransferase (AST) and bilirubin were observed in a small number of participants across treatment groups including placebo in the FTIH study of single doses of GSK2330811 in healthy participants. Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_02, 2019].	• Participants will be screened for HCV and HBV and excluded if positive. • Participants will be excluded if ALT or bilirubin ≥ 1.5x upper limit of normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%), • Standard GSK phase 1 monitoring of liver chemistry and criteria for enhanced liver chemistry monitoring and follow up Assessments will be implemented.
Reproductive Toxicity	• Animal reproductive toxicity studies have not yet been carried out with GSK2330811. • Animal reproductive toxicity studies have been carried out for GSK315234, another IgG anti-OSM monoclonal antibody. GSK2330811 and GSK315234 antibodies bind different epitopes but have similar affinity for OSM in the animal model used. No GSK315234 related effects on pregnancy, embryofoetal development, parturition and lactation and on survival, growth and postnatal development of the offspring were noted at doses up to 150 mg/kg/month, the highest dose tested.	• The study will only recruit male participants. • There are no specific contraception requirements for males participating in this study.
Carcinogenicity	• There is conflicting evidence for the role of OSM in cell proliferation in metastatic cancer. Data are primarily from isolated cell-line systems and, depending on the cell type, OSM has been shown to act both as an anti-proliferative and a proliferative factor.	• Participants with a history of carcinoma in situ and malignant disease will be excluded with certain exceptions as described in Section 5.2.

2.3.2. 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 CD and SSc.

2.3.3. Overall Benefit: Risk Conclusion

The safety of each individual participant has been prioritised and the eligibility, monitoring, enhanced monitoring and study level stopping criteria described in Section 7 have been designed to minimise risks to participants associated with exposure to GSK2330811. Taking into account these measures designed to minimise risks, the potential risks identified in association with GSK2330811 are justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
• To evaluate the safety and tolerability of a single SC dose of GSK2330811 in healthy Japanese participants	• Number of participants reporting AEs. • Number of participants reporting SAEs. • Number of participants with vital signs (blood pressure, heart rate, body temperature) reaching a threshold of potential clinical importance. • Number of participants with treatment emergent abnormal ECG findings. • Number of participants with CTCAE grade 1 or higher safety laboratory results (clinical chemistry, haematology values where CTCAE grading applies). • Number of participants with treatment emergent abnormal urinalysis findings.
Secondary	Secondary
• To evaluate the pharmacokinetic (PK) profile of a single SC dose of GSK2330811 in healthy Japanese participants	• Pharmacokinetic parameters (Cmax, AUC, CL/F, Tmax, $t_{1/2}$, Vss/F).

Objectives	Endpoints
• To assess the potential for anti-drug antibody (ADA) formation following a single SC dose of GSK2330811 in healthy Japanese participants	• Number of participants with anti-GSK2330811 antibodies
• To assess effects of GSK2330811 on platelets and haemoglobin in healthy Japanese participants	• Platelet nadir • Time to platelet nadir • Haemoglobin nadir • Time to haemoglobin nadir
Tertiary/Exploratory	Tertiary/Exploratory
• To explore the PD and the PK/PD relationship for GSK2330811 in the blood of healthy Japanese participants	• Serum levels of free OSM • Serum levels of total OSM • Levels of Thrombopoietin (TPO) • Levels of Erythropoietin (EPO)

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind (sponsor-open), placebo-controlled, single-centre study with single SC doses of GSK2330811 administered to healthy male Japanese participants.

- Participants will attend a screening visit at the clinical unit within 30 days of Study Day 1. If eligible for the study, participants will return on Day -1 for overnight admission to the unit.
- Participants will be randomized to either GSK2330811 or placebo in an approximate ratio of 7:3.
- Approximately 10 eligible participants will be admitted to the clinical unit on the day prior to dosing (Day-1). On Day 1, each participant will receive a single SC dose of GSK2330811 or placebo, administered as three separate SC injections. Participants will then remain as an in-patient until discharged on Day 2 after assessments have been performed.
- Participants will then return to the clinical unit for outpatient visits as described in the SoA.
- The final follow up visit will be at the clinical unit on Day 126.
- The maximum dose will not exceed 450 mg SC.

4.2. Number of Participants

Approximately ten participants will be enrolled and dosed (7 GSK2330811: 3 Placebo) with a view to ensuring 8 are evaluable (6 GSK2330811: 2 Placebo). See Section 9.2 for details. Evaluable is defined as a participant who has received a full dose and has attended all visits up to Day 56 and at least one of Day 84 or Day 126.

In rare instances, a participant may not be able to receive all 3 required injections and will receive a partial dose. In such circumstances, the participant will not be considered evaluable, but will be encouraged to remain in the study for the planned duration.

If any participant is non-evaluable for any reason, the participant may be replaced at the discretion of the sponsor in consultation with the investigator and assigned to the same treatment.

Up to a maximum of 14 participants may be enrolled and dosed.

4.3. Intervention Groups and Duration

This study will include a single cohort of approximately 10 participants randomised to a single dose of 450 mg SC GSK2330811 or placebo in a 7:3 ratio (active: placebo).

The study duration, including screening and follow-up, is not expected to exceed 163 days for any participant in the study. The follow-up may be extended if a SAE has not resolved by the final scheduled visit (see Section 8.3.3 and Section 10.3.3).

4.4. Scientific Rationale for Study Design

The proposed 450 mg single SC dose in Japanese participants is anticipated to result in exposure comparable to the 6 mg/kg (average 417 mg, range 375-443 mg) single SC dose tested in Caucasian participants in the FTIH study 201246 allowing a comparative assessment of ethnic sensitivity in terms of safety, tolerability and PK and PD in a Japanese population. Furthermore, a dose of 450 mg SC aligns with the highest anticipated dose to be administered in the global clinical studies with GSK2330811.

In addition, this study will be conducted in healthy male participants for the following reasons:

- Patients with inflammatory and fibrotic diseases may have existing comorbidities or be taking concomitant medications that may confound the analysis.
- It is anticipated that patients would derive little or no benefit from a single dose of GSK2330811, but that taking part in the study might interfere with their ability to receive other potentially efficacious therapies.
- Animal reproductive toxicity studies have not yet been carried out with GSK2330811 and therefore the benefit-risk of enrolling women of child-bearing

potential in this study, where they are unlikely to derive any direct benefit from a single dose of GSK2330811, does not support their inclusion. Moreover, enrolling only male participants will facilitate comparison with data from study 201246, a single-dose FTIH study of GSK2330811 in predominantly male Caucasian participants [Reid, 2018].

This study will include a placebo arm to ensure that the treatment-attribution of adverse events (AEs) is appropriately blinded and to provide control data for the PD and safety laboratory assessments.

The duration of follow-up will be about 126 days, which will be approximately 5 half-lives of GSK2330811 (half-life of between 19 to 25 days) [GlaxoSmithKline Document Number 2016N284919_02, 2019].

Exploratory endpoints have been chosen to confirm target engagement and further investigate PK/PD relationships in the blood.

4.5. Justification for Dose

To date, GSK2330811 has been administered as single SC doses to healthy participants (0.1-6 mg/kg) in the FTIH study 201246. In the highest dose cohort in study 201246, the average administered dose was 417 mg (range 375-443 mg). GSK2330811 is currently being tested in a repeat SC dose study (201247) of participants with systemic sclerosis (100 and 300 mg every other week for 6 doses).

The 450 mg single SC dose proposed for this study in healthy Japanese participants is anticipated to result in exposure comparable to the 6 mg/kg single SC dose tested in healthy Caucasian participants in study 201246. The 450 mg single SC dose is 47x lower than the NOAEL dose for non-pharmacology-related findings (300 mg/kg/week, highest dose tested) observed in the 26-week toxicity study in monkeys. Safety margins for predicted exposure in this study are summarised in Table 1. Predicted exposure was simulated using the minimal Physiologically Based Pharmacokinetic (mPBPK) model developed from data from study 201246 [Reid, 2018]. Clearance and volume were allometrically scaled assuming median body weight for Japanese living in the Western hemisphere equal to 64.2 kg (based on 15 Japan PK studies run by GSK in the Western hemisphere) and minimum body weight equal to 45 kg, as per study inclusion criteria. Allometric scaling is likely to over-predict exposure.

Table 1 Safety margins for predicted exposure for 450 mg SC single dose vs measured exposure in Study 201246 and 26-weeks toxicology study

Body weight (kg)	Predicted for 450 mg SC SD	Observed in 201246[1]	Fold difference: observed in 201246[2]/ Predicted for 450 mg SC SD	NOAEL[3]	Fold difference: NOAEL[3]/Predicted for 450 mg SC SD
Parameter: Cmax (ug/mL)					
64.2	33	36.4 (28.7-48.9)	1.1x	9710	294x
45	39		0.9x		249x
Parameter: AUC (mg.hr/mL) [4]					
64.2	33	27.7 (19.8-37.7)	0.8x	1390	42x
45	43		0.6x		32x

[1] Shown are observed geomean (range) for 6 mg/kg single dose (SD) SC. [2] Calculated using geomean observation in 201246. [3] NOAEL for non-pharmacodynamic related findings is 300 mg/kg/wk SC, which is the highest dose tested in the 26-weeks toxicology study in monkey. Shown are mean, gender averaged, exposures at Week 25. [4] Note that different AUCs are shown: Predicted for 450 mg SC SD: $AUC_{(0\text{-}inf)}$-; 201246: $AUC_{(0\text{-}inf)}$; NOAEL: $AUC_{(0\text{-}tau)}$, where tau is 1 week.

The safety and tolerability of ascending single SC doses of GSK2330811 in the range of 0.1 mg/kg to 6 mg/kg were studied in study 201246. GSK2330811 at these doses was generally well tolerated in healthy participants. Reversible, dose-dependent decreases in platelet counts were observed from the 1 mg/kg to the 6 mg/kg dose levels with recovery evident between Days 28 to 35. A reduction in haemoglobin from baseline values was observed in the GSK2330811 6 mg/kg group with all participants returning to within the normal range by Day 133. Further details can be found in Section 5 of the IB [GlaxoSmithKline Document Number 2016N284919_02, 2019].

The effect of GSK2330811 on platelets and haemoglobin is anticipated to be comparable in Japanese and Caucasian participants, since average exposure and target engagement are predicted to be comparable in the two populations. At the 6 mg/kg (average 417 mg) dose studied in study 201246, median maximum target engagement (TE) was 90% in serum. Therefore, a dose of 450 mg SC is appropriate to investigate the saturated PK/TE relationship. Furthermore, a dose of 450mg SC is the highest dose to be administered in the global clinical studies with GSK2330811.

4.6. End of Study Definition

A participant is considered to have completed the study if he has completed the treatment and follow-up phases of the study including the last scheduled procedure shown in the SoA.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests and 12-lead ECGs
3. A participant with a clinical abnormality or laboratory parameter(s) outside the reference range for the healthy population being studied that is not specifically listed in the inclusion or exclusion criteria may be included if the investigator and GSK Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or interpretation.

Weight

4. Body weight ≥45 kg and body mass index (BMI) within the range 18.5-29.9 kg/m^2 (inclusive).

Sex

5. Male

Informed Consent

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

Geographical Ancestry

7. 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.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Sensitivity to any of the study treatments or components there of (including humanised monoclonal antibodies) or history of severe post treatment hypersensitivity reactions including erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis and exfoliative dermatitis.

2. Any other history of significant allergy that in the opinion of the investigator contraindicates their participation in this study.

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 prior to Day 1. Topical treatments may be allowed at the Investigator's discretion (in consultation with the Medical Monitor).

    b. A history of opportunistic or recurrent infections, as determined by the investigator.

    c. Currently active or unresolved infection. Participants with 'trivial' infections such as tinea pedis may be eligible at the discretion of the investigator.

    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).

        NOTE: In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once and will be eligible if the second test is negative.

4. Any planned major surgical procedure during the study.

5. A history of haematological disease, for example (but not limited to): significant anaemia, platelet disorders including drug-induced thrombocytopaenia or primary immune thrombocytopaenia and coagulation disorders including von Willebrand's disease.

6. A history of carcinoma in situ and malignant disease, with the exception of adequately treated non-metastatic basal or squamous cell cancer of the skin that has been fully treated and shows no evidence of recurrence after 3 years.

7. QTc >450 msec at screening.

   NOTE: The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), or another method, machine-read or manually over-read. The same correction is to be used throughout the study.

Prior/Concomitant Therapy

8. 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 Day 1 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.

   NOTE: Paracetamol at doses of ≤4 grams/day, and occasional use of NSAIDs at licensed doses, are permitted.

9. Received live vaccination within 4 weeks prior to Day 1, or any plan to receive a live vaccination during the study (i.e. up to and including to the last follow-up visit).

Prior/Concurrent Clinical Study Experience

10. Participation in a clinical trial and has received an investigational medicine product (IMP) within the following time period prior to Day 1: 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 Day 1.
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. Platelet count or haemoglobin below the normal range at any time during screening.
14. ALT >1.5x ULN at any time during screening.
15. Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at any time during screening.
16. Presence of Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb), or positive HCV antibody result at screening

    NOTE: Participants with positive HCV antibody due to prior resolved disease can be enrolled only if a confirmatory negative HCV RNA test is obtained.

17. Positive HIV antibody test at screening.
18. Positive pre-study drug/alcohol screen.

    NOTE: Retesting of diagnostic assessments in the case of potentially spurious results or sample handling errors is allowed during the screening period. See Section 5.4 for details.

Other Exclusions

19. History of regular alcohol consumption within 6 months of the screening visit in excess of an average weekly intake of >21 units. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
20. Planning to travel to regions of high endemic infection, as determined by the investigator, for the duration of the study.
21. 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.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants will be required to fast for approximately 12 hours (no food or drink, except water) prior to collection of the Day 1 and Day 21 clinical chemistry blood sample. There will be no other caffeine, xanthine or dietary restrictions for the rest of the study.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be permitted while they are in the clinical unit. Participants will abstain from alcohol for 24 hours prior to clinic visits. Thereafter a weekly intake of ≤21 Units of alcohol is permitted.

5.3.3. Activity

- Participants will abstain from strenuous exercise 24 hours prior to each blood collection for clinical laboratory tests.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled (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, any protocol deviations and any SAEs.

Repeat assessments during the screening period: Assessments, including laboratory assessments, may be repeated once if determined necessary by the investigator, for example: (a) in cases of technical malfunction (e.g. loss of laboratory specimen), (b) in the event of a value close enough to the exclusionary threshold that it may reasonably lie within the degree of variability of the assay or an indeterminate result; (c) if there is

reason to believe the result may be false (i.e. contradicts recent result for the same parameter). These are repeat assessments and not rescreening events. If the original result was exclusionary and is confirmed by repeat testing, the participant will be excluded.

Rescreening: Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the investigator. Rescreened participants will be assigned a new participant number.

6. 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.

6.1. Study Intervention(s) Administered

This study will use a pre-filled syringe (PFS): Becton Dickinson's UltraSafe Plus Safety Syringe Device. Instructions for use of the PFS medical device are provided in the Study Reference Manual (SRM).

Intervention Name	GSK2330811	Placebo
Type	Drug	Placebo
Dose Formulation	50mM Sodium Acetate Trihydrate, 51mM Sodium Chloride, 1% (w/v) L-Arginine, 0.05mM Edetate Disodium Dihydrate (EDTA) and 0.02% Polysorbate 80 in Water for Injection USP, pH 5.5	Normal saline (0.9% sodium chloride)
Unit Dose Strength(s)	150mg/ml	N/A
Dosing Instructions	Administered by study personnel. 3 injections to be used to provide 450mg SC dose.	Administered by study personnel. 3 injections will be used to match active doses administered.
Route of Administration	SC injection to abdomen	SC injection to abdomen
IMP and Non-investigational medicinal product (NIMP)	IMP	NIMP

Intervention Name	GSK2330811	Placebo
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labelling	Study intervention will be provided in a pre-filled safety syringe. Label content will be in accordance with the country's regulatory requirements	Study intervention will be provided in a pre-filled safety syringe. Label content will be in accordance with the country's regulatory requirements
[Current/Former Name(s) or Alias(es)]	Anti-OSM	N/A

GSK2330811 is a humanised monoclonal antibody and all formulation ingredients have been previously used in the clinic.

SC GSK2330811 is administered as multiples of 150 mg injections, each provided as a pre-filled safety syringe.

In an individual participant, injections should be administered into the abdomen and should be separated by a minimum of 2 cm. The location of the injections (abdominal quadrant) will be recorded.

6.2. Preparation/Handling/Storage/Accountability

Each syringe will be supplied as a single PFS within a labelled carton, detailing the appropriate content according to the country's regulations.

Study treatment will be stored in the refrigerator. The PFS must be allowed to come up to room temperature for at least 30 minutes after taking out of the refrigerator prior to use. Refer to the SRM for further details.

Any malfunctions of the PFS must be documented and reported throughout the study (see Section 10.7 for reporting of syringe deficiencies and malfunctions).

The following will also apply in the study:

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 SRM.

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.

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.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomisation and Intervention Assignment

Participants who meet the screening eligibility criteria will be randomised to a treatment group through the Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to the site.

Once assigned, a randomisation number must not be reassigned to another participant in the study

6.3.2. Blinding

This will be a double blind (sponsor-open) study with both the investigator and participant blinded to study treatment. Site personnel will remain blinded.

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 participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.
- If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant.
- If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind.
- The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.
- A participant may continue in the study if that participant's intervention assignment is unblinded.

- GSK's Safety and Medical Governance (SMG) staff may unblind the intervention 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 intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

- Sponsor-open refers to the potential need of the sponsor to unblind single or multiple participants at the request of the GSK2330811 Safety Review Team (SRT) (see Section 10.1.5) to investigate important safety concerns. This would be done in accordance with GSK standard operating procedures, is expected to be very uncommon, and will be implemented in such a way as to maintain the integrity of the study as much as possible.

6.3.2.1. Risk of Inferred Unblinding

The treating physician and/or delegate (including the study nurse) will have sight of safety laboratory results to fulfil their responsibility for the medical care of study participants. Therefore, in this study there is a risk that the physician and/or delegate may infer a participant's treatment allocation through this knowledge.

Sites will be required to make every effort to ensure that the results of study laboratory tests are not proactively communicated to participants during the study unless essential for clinical care.

Study monitors, through their review of safety laboratory results, are also at risk of inferring a participant's treatment.

PK and Free and Total OSM results that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of the 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.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) 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 GSK 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 GSK Medical Monitor, the medication will not interfere with the study.

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

6.6. Dose Modification

No dose modifications are planned.

6.7. Intervention after the End of the Study

This is a single dose study in healthy participants. No study intervention will be provided following the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

This is a single dose study. In rare instances a participant may not be able to receive all 3 injections and it may be necessary for the participant to permanently discontinue study intervention. If study intervention is discontinued, the participant will remain in the study for the planned duration.

7.1.1. Study Stopping Criteria

If any of the following occur, the study will be temporarily halted:

- Any participant experiences a SAE that can be reasonably attributed to GSK2330811.

- Two or more participants experience a severe adverse event that can be reasonably attributed to GSK2330811.

- Any participant experiences a CTCAE Grade 3 or greater reduction in platelet count (< $50x10^9$/L) or haemoglobin (< 80 g/L). This should be confirmed by a repeat blood sample if there is any concern that the result may be spurious.

The Competent Authority and the Ethics Committee will be notified of a Temporary Halt. No further participants will be dosed until a full safety review by relevant GSK personnel has taken place. If, following the safety review, a decision is made to restart dosing, this will be based on an updated assessment of the benefit risk and will only occur after Competent Authority and Ethics Committee approval via a substantial amendment.

7.1.2. Liver Chemistry Enhanced Monitoring Criteria

Phase 1 Liver chemistry increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

- Refer to Section 10.4 for liver safety required actions and follow-up assessments.
- Any participant meeting the liver chemistry criteria (ALT ≥3x ULN) will have enhanced monitoring as detailed in Section 10.4. The participant should continue in the study, given this is a single dose study.
- Liver events meeting SAE criteria will be managed as detailed in Section 7.1.1 Study Stopping Criteria.

7.1.3. QTc Enhanced Monitoring Criteria

The same QT correction formula must be used for each individual participant to determine eligibility and for all monitoring throughout the study. The formula must not be changed or substituted once the participant has been enrolled.

For participants that meet either of the bulleted criterion below, additional monitoring will be undertaken until the QTc value is no longer clinically significant. The frequency of this monitoring and the decision as to when the QTc value is no longer clinically significant will be at the discretion of the investigator. The participant should continue in the study, given this is a single dose study.

- QTc >500 msec.
- Change from baseline: QTc >60 msec.

The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief recording period.

7.1.4. Haematological Enhanced Monitoring Criteria

Any participant with platelet count $<75x10^9$/L (CTCAE Grade2) must have platelet count assessed at least weekly until platelet count is $\geq 75x10^9$/L. This may necessitate unscheduled assessments.

Any participant with a haemoglobin <100 g/L (CTCAE Grade2) must have haemoglobin assessed at least weekly until haemoglobin is ≥100g/L. This may necessitate unscheduled assessments.

7.2. Participant 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 withdrawal from the study, if possible, an early withdrawal visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently withdrawn 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.

7.3. 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 the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness 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 or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- 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.
- 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.

8.1. Efficacy Assessments

Efficacy assessments are not applicable to this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (at screening only) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

8.2.2. Vital Signs

- Temperature (tympanic), pulse rate and blood pressure will be assessed.
- Vital signs will be measured in a semi-supine position after 5 minutes rest in a quiet setting without distractions.

- Vital signs will be measured with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs are to be taken before blood collection for laboratory tests.

8.2.3. ECGs

- Triplicate 12-lead ECGs will be obtained in a semi-supine position as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.3 for additional QTc readings that may be necessary.
- The *same* QT correction formula *must* be used for *each individual participant* to determine study eligibility and enhanced monitoring, and this formula may not be changed or substituted once the participant has been screened.
- Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.2.4. 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 case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal within 126 days after the last dose of study intervention should be repeated periodically until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor. This monitoring may extend beyond the final scheduled follow-up visit. Also see Section 7.1.2 and Section 7.1.4 for protocol defined enhanced monitoring requirements for specific assessments.
- 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.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Injection Site Reaction Assessments

Trial staff will apply light pressure at the injection site and record any tenderness, erythema and induration in accordance with the SoA and SRM.

8.2.6. Hypersensitivity Reactions

As GSK2330811 is a 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 local reaction during dosing, study intervention administration may be reinitiated (with appropriate pre-medication if thought necessary) 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 an 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 according to relevant local/national guidelines if there is any compromise of the participant's airway, breathing or circulation:
- Provide high concentration oxygen via a non-rebreather 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 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.

8.3. Adverse Events and Serious Adverse Events

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

For the purpose of reporting safety events related to the PFS, the definitions of device-related safety events, (adverse device effects (ADEs) and serious adverse device effects (SADEs), can be found in Section 10.7, (Appendix 7). PFS deficiencies are covered in Section 8.3.5.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) and identified by the investigator/designee through clinical examination and review of laboratory investigations.

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 withdraw from the study (see Section 7).

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

- All SAEs will be collected from the signing of the ICF until the final follow-up visit.
- All AEs will be collected from the start of intervention until the final follow-up visit (Section 1.3).
- 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.

8.3.2. 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.

8.3.3. 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 SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). This may require follow-up beyond the final scheduled follow-up visit. Further information on follow-up procedures is given in Appendix 3.

8.3.4. 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 SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pre-Filled Syringe Deficiencies

PFS are being provided for use in this study for administering the study treatment. In the event that a deficiency or a malfunction occurs with the PFS, in order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of PFS deficiencies that occur during the study.

For the purpose of reporting deficiencies and malfunctions, the definition of a Medical Device Deficiency can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.5.1. Time Period for Detecting Pre-Filled Syringe Deficiencies

- PFS deficiencies will be detected, documented, and reported during all periods of the study in which the medical device is used.
- The method of documenting PFS deficiencies or malfunctions is provided in Appendix 7.

8.3.5.2. Follow-up of Pre-Filled Syringe Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.5.3. Prompt Reporting of Pre-Filled Syringe Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor within 72 hours after the investigator becomes aware of a deficiency or malfunction.
- The PFS Deficiency/Malfunction Report Form will be sent to the sponsor.
- The sponsor will be the contact for the receipt of PFS deficiency reports.

8.3.5.4. Regulatory Reporting Requirements for Pre-Filled Syringe Incidents

- The PFS to be used in the study is a combined medicinal product/medical device. The investigator will promptly report all deficiencies occurring with any medical device component provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of any medical device component deficiencies to the IRB/IEC.
- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Treatment of Overdose

For this study, any potential dose of GSK2330811 greater than 450 mg will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities weekly for at least 4 weeks or as otherwise advised by the Medical Monitor.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

As this is a single dose study, in the event of an overdose no further study treatment will be administered to the participant.

8.5. Pharmacokinetics

- Approximately 2 mL EDTA blood will be collected at the time-points listed in the SOA for determination of GSK2330811 plasma concentrations.

- Instructions for the collection and handling of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.

- GSK2330811 plasma concentration analysis will be performed under the control of In Vitro/In Vivo Translation/Bioanalysis, Immunogenicity, Biomarkers (IVIVT/BIB), GlaxoSmithKline. Plasma concentrations of GSK2330811 will be determined using approved bioanalytical methodology. The bioanalytical site will be detailed in the SRM and raw data will be archived by the bioanalytical site listed in the SRM.

- Once the plasma has been analysed for GSK2330811, with the participant's consent (see Section 10.1.3), residual samples may be stored and used for research to develop methods and assays including potential diagnostics related to targeting OSM in a range of potential conditions or to further understand the mechanism of action of GSK2330811.

8.6. Pharmacodynamics

8.6.1. Total and Free OSM

Pharmacodynamic parameters of GSK2330811 target engagement with OSM will be assessed by measuring free and total OSM in serum.

- Approximately 2 mL blood will be collected and processed to serum at the time-points listed in the SOA for determination of total and free OSM.
- Instructions for the collection and handling of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Sample analysis will be performed under the control of In Vitro/In Vivo Translation/Third Party Resourcing (IVIVT/TPR), GlaxoSmithKline. Plasma concentrations of GSK2330811 will be determined using approved bioanalytical methodology. The bioanalytical site will be detailed in the SRM and raw data will be archived by the bioanalytical site listed in the SRM.
- In addition, with the participant's consent (see Section 10.1.3), residual samples may be stored and used for research to develop methods and assays including potential diagnostics related to targeting OSM in a range of potential conditions or to further understand the mechanism of action of GSK2330811.

8.6.2. Erythropoietin (EPO) and Thrombopoietin (TPO)

Blood samples will be collected for biomarker assessments related to the mechanism of anaemia and thrombocytopenia. These may include (but are not restricted to) EPO and TPO.

- Approximately 2 mL blood will be collected for each biomarker listed above at the time-points listed in the SOA to evaluate their association with the observed clinical responses to GSK2330811.
- Instructions for the collection and handling of biological samples will be provided in the SRM. The date of each sample will be recorded.
- In addition, with the participant's consent, residual samples may be stored and used for research to develop methods and assays including potential diagnostics related to targeting OSM in a range of potential conditions or to further understand the mechanism of action of GSK2330811.

8.7. Biomarkers

No additional samples other than those detailed in Section 8.6 will be analysed.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Immunogenicity Assessments

Blood samples will be collected for immunogenicity assessment.

- Approximately 4 mL blood will be collected and processed to serum at the time-points listed in the SOA for the determination anti-GSK2330811 antibodies.
- Instructions for the collection and handling of biological samples will be provided in the SRM. The date of each sample will be recorded.
- Sample analysis will be performed using a tiered approach involving screening, confirmation and titration [EMA, 2017;FDA, 2019] under the control of IVIVT/BIB, GlaxoSmithKline. The bioanalytical site will be detailed in the SRM and raw data will be archived by the bioanalytical site listed in the SRM.
- If sera contain potential anti-GSK2330811 antibodies in the screening assessment, they will be confirmed by immune-competition using excess drug, followed by a titration assay. Results will include the incidence of immunogenicity and titres.
- Samples testing positive for anti-GSK2330811 antibodies may be further characterised for the presence of GSK2330811 neutralizing activity (NAb).

8.10. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of this study is to assess the safety, and tolerability of single SC doses of GSK2330811 in healthy Japanese participants. No formal hypotheses are being tested in this study.

9.2. Sample Size Determination

There will be a minimum of 10 Japanese participants. The participants will be randomised in the ratio 7:3 to GSK2330811 (450 mg) or placebo.

From the number of adverse events of a specific type observed in 7 participants receiving GSK2330811, statistical inferences can be made about the 95% Credible Interval of the true event rate, as shown in Table 2, specifying a prior distribution (Beta [1,1]). The 95% CrI for 6 participants is also presented, as the sample size was defined with a view to

ensuring at least 6 participants receiving GSK2330811 are evaluable. Table 2 shows that if 0 particular safety events are observed out of 7 participants in the GSK2330811 group, the upper limit of the 95% Credible Interval indicates that a true event rate of 37% could not be ruled out.

Table 2 Upper 95% Credible Limit of the True Event Rate based on 7 participants on GSK2330811 completing the study

Observed events / participants in cohort	Lower 95% Credible Limit of true event rate	Upper 95% Credible Limit of true event rate
0/7	0.3%	37%
1/7	3.2%	53%
2/7	8.5%	65%
0/6	0.4%	41%
1/6	3.7%	58%
2/6	9.9%	71%

The values in Table 3 are the geometric means of PK parameters observed in the FTIH study 201246 following GSK2330811 SC administration:

Table 3 AUC and Cmax Geometric Means and Percent Coefficient of Variation (%CV_b) Observed in Caucasian PK Study 201246

Treatment group	Value (%CV_b)	
	AUC (0-inf) (h*ug/mL)	Cmax (ug/mL)
0.1 mg/kg	615 (26.2)	0.6 (32.3)
0.3 mg/kg	1605 (21.6)	1.5 (42.7)
1 mg/kg	5316 (42.5)	5.7 (43.5)
3 mg/kg	14656 (21.6)	19.0 (42.7)
6 mg/kg	27681 (23.3)	36.4(22.9)

The mean baseline weight in the 201246 study was 69.5kg and so the 6 mg/kg dose corresponds to an average dose of 417 mg; therefore, the PK parameters and CV_b %'s presented in Table 3 for the 6 mg/kg group are a good approximation for a dose of 450 mg.

Simulations were performed to determine the sample size based on comparing PK exposure in Japanese to PK exposure in Caucasians. The simulations were based on the data from the 6 participants who received 6 mg/kg of GSK2330811 in 201246, whose geometric mean of $AUC_{(0\text{-inf})}$ was 27681 h*µg/mL (95% Confidence interval (CI): 21748 to 35233). Assuming the true $AUC_{(0\text{-inf})}$ for the Japanese participants is the same as that of the 6 mg/kg dose from 201246 and a standard deviation on the $\log_e$ scale of 0.23, the probability that the observed median will be within the 95% CI of the 6 mg/kg group is 97.5% for 6 evaluable participants receiving GSK2330811 and 97.8% for 7 evaluable participants receiving GSK2330811. The probability that the median $AUC_{(0\text{-inf})}$ will be within 0.5-2 fold change of the geometric mean from the 6 mg/kg group (13841 to 55363 h*ug/mL) is 100% for either 6 or 7 evaluable participants receiving GSK2330811.

Additional simulations were performed factoring in the effect of body weight on exposure utilising the mPBPK model developed using data from study 201246. If the true $AUC_{(0\text{-inf})}$ is affected by body weight according to allometric scaling and intra-individual variability is 30% (as estimated by the mPBPK model), the probability that the geometric mean of $AUC_{(0\text{-inf})}$ is within 0.5-2 fold compared to that observed in study 201246 remains 100% for 6 evaluable participants receiving GSK2330811.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who signed the ICF and were screened for eligibility.
Enrolled	All participants who signed the ICF and are randomized into the study.
Safety	All randomized participants who received at least one dose of study treatment. Participants will be analysed according to the treatment they received. Note: In the very unlikely case a participant is not randomized but receives at least one dose of study treatment, these participants will be listed separately.
Pharmacokinetic	All participants in the Safety population who received at least one active dose of study treatment and had at least 1 non-missing PK assessment (Non-quantifiable values will be considered as non-missing values). Participants will be analysed according to the study treatment they received.

9.4. Statistical Analyses

The Reporting Analysis Plan (RAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1. General Considerations

No formal hypothesis testing will be performed in this study. Summary statistics and graphs will be presented where appropriate.

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 (or

Day -1 where applicable) assessments are assumed to be taken prior to first dose and used as baseline.

If baseline data is missing, no derivation will be performed, and baseline will be set to missing.

9.4.2. Primary Endpoint(s)

Analysis	Details
Endpoints	• Number of participants reporting AEs and SAEs • Number of participants with vital signs (blood pressure, heart rate, body temperature) reaching a threshold of potential clinical importance • Number of participants with treatment emergent abnormal ECG findings. • Number of participants with CTCAE grade 1 or higher safety laboratory results (clinical chemistry, haematology values where CTCAE grading applies). • Number of participants with treatment emergent abnormal urinalysis findings.
Analysis	• For count data, the number and percentage of participants will be presented. • In addition, where continuous data is available, descriptive statistics (i.e. n, arithmetic mean, standard deviation, minimum, median, and maximum) of both raw and change from baseline data will be also presented. • CTCAE criteria (version 5) will be used to categorise laboratory safety data.
• Statistical Analysis (Modelled)	• No statistical modelling is planned.

9.4.3. Secondary Endpoint(s)

9.4.3.1. Pharmacokinetic parameters

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" population. Individual plasma concentration-time data will be graphically displayed and summary statistics will be produced by time point. Plasma GSK2330811 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 pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration-time curve ($AUC_{[0\text{-}t]}$, $AUC_{[0\text{-}inf]}$), terminal half-life ($t_{1/2}$), apparent volume of distribution at steady state (Vss/F) and apparent systemic clearance (CL/F).

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, standard deviation on the log scale and %CVb will be provided.

Full details of planned secondary analysis will be specified in the RAP.

9.4.3.2. Other secondary endpoints

The number and percentage of participants with confirmed positive anti-GSK2330811 antibodies will be presented. Where applicable the titres will be listed.

Descriptive statistics (n, arithmetic mean, standard deviation, median, minimum and maximum) will be calculated for nadirs (for platelet count and haemoglobin).

Descriptive statistics (n, median, minimum, maximum and range) will be calculated for time to nadir (for platelet count and haemoglobin).

Full details of planned secondary analysis will be specified in the RAP.

9.4.4. Exploratory Endpoints

- Summary statistics will be produced where appropriate by time point and treatment group.
- Graphical displays will be produced over time for serum free and total OSM, TPO and EPO levels.
- Exploratory PK/PD analyses, if data permit, may be completed on selected free and total OSM measurements to examine the relationship between plasma concentrations of GSK2330811, and target OSM concentration (free and total).
- Exploratory PK/PD analyses, if data permit, may be conducted on the platelet endpoint to examine the relationship between plasma concentrations of GSK2330811, and platelet count.

Full details of planned exploratory analysis will be specified in the RAP.

9.5. Interim Analyses

No interim analyses are planned.

9.6. Interim Data Review Committee

An interim data review committee will not be required.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. 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 International Council of Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, 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.

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her 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, where applicable, 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 or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK2330811 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK2330811 approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate tick box will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her 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.

10.1.5. Committees Structure

In line with routine pharmacovigilance, oversight of study safety will be provided by the GSK2330811 Safety Review Team (SRT). The SRT will conduct in-stream periodic review of blinded safety data including AEs, SAEs, vital signs and laboratory data. Ad hoc reviews may be scheduled if required and under certain circumstances the SRT may request unblinding of events to address an emerging safety concern (see Section 6.3.2).

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. 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 participant-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.

10.1.7. 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 Clinical Study Report (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.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- 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.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

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.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant follow-up

10.1.10. Publication Policy

- The results of this study will be progressed for publishing and may be 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit Reticulocyte % Reticulocytes	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Urea	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Albumin
	Glucose[3]	Calcium	Alkaline phosphatase	Lipids (fasted)[2]: Total Cholesterol HDL LDL Triglycerides
	INR[4]	APTT[4]		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	**Parameters**
Other Screening Tests	• Breath alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb], and HCV antibody) • 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 7 and Appendix 7 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. Blood for lipids (fasted) will be taken at pre-dose on day 1 and at day 21
3. Non-fasting sample except for pre-dose on day 1 and day 21.
4. Blood for INR and APTT will be taken at screening.

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

10.3.1. 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. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless 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.

10.3.2. 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:

- Results in death
- 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 fulfills 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 or significant 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, diarrhea, 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.

10.3.3. 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 Investigator's Brochure (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.

10.3.4. 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 IP/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 SRM.

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.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Not applicable.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver chemistry stopping criteria and required follow up assessments have been designed to assure participant safety and to evaluate liver event etiology

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >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≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [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</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 pharmacokinetic (PK) analysis, as soon as possible and at least within 7 days of liver event[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• 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 acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:**
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [James, 2009]. • 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 participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. 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 ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN 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 participants receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; HCV 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. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.7. Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The device to be used in this study is a combination medicinal product; the PFS
- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to the PFS provided for use in this study.

10.7.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of SAE, SADE and USADE

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).

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. 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 2. A permanent impairment of a body structure or a body function, 3. Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

USADE definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the sponsor AE/SAE/device deficiency CRF page. • There may be instances when copies of medical records for certain cases are requested by the sponsor. 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 the sponsor. • 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. • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one 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 a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs 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.
- Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- 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 Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE/device deficiency, the investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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 a 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/SAE/device deficiency
• 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/SAE/device deficiency 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.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an 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. • 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 GSK medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the GSK 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.

10.7.6. Reporting of SADEs

SADE Reporting to GSK
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in the SRM.

10.8. Appendix 8: Country-specific requirements

Non applicable

10.9. Appendix 9: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibody
ADE	Adverse Device Effect
AE	Adverse event(s)
ALT	Alanine aminotransaminase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
AUC	Area under the curve
AUC(0-inf)	Area under the plasma concentration time-curve from time zero to infinity
AUC(0-t)	Area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration
BMI	Body Mass Index
CA	Competent Authority
CD	Crohn's Disease
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV_b	Coefficients of variation
EC	Ethics committee
ECG	Electrocardiogram

eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EPO	Erythropoietin
F	Bioavailability
FTIH	First Time In Human
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator('s) Brochure
ICF	Informed Consent Form
ICH	International Council of Harmonization
IDRC	Interim Data Review Committee
IEC	Independent Ethics Committees
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Boards
IVIVT/BBI	In Vitro/In Vivo Translation/ Bioanalysis, Immunogenicity, Biomarkers
IVIVT/TPR	In Vitro/In Vivo Translation/Third Party Resourcing
IWRS	Interactive Web Response System
KLH	Keyhole Limpet Hemocyanin

LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MCH	Mean Corpuscular Haemoglobin
mPBPK	minimal Physiologically Based Pharmacokinetic
MSDS	Material Safety Data Sheet
NIMP	Non-investigational medicinal product
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
OSM	Oncostatin M
PD	Pharmacodynamic
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	Corrected QT interval (Fridericia's formula)
RAP	Reporting Analysis Plan
RBC	Red Blood Cell
SADE	Serious adverse device effect
SAE	Serious adverse event(s)
SC	Subcutaneous
SD	Single dose
SMG	Safety and Medical Governance
SoA	Schedule of Activities
SRM	Study Reference Manual
SSc	Systemic Sclerosis
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis

TE	Target Engagement
Tmax	Time of occurrence of Cmax
TMDD	Target-mediated drug disposition
TPO	Thrombopoietin
ULN	Upper limit of normal
USADE	Unexpected serious adverse device effect

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
QuantiFERON
UltraSafe Plus

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