TITLE PAGE

Protocol Title: A multi-centre, randomized, double-blind (sponsor open), placebo-controlled, repeat-dose, proof of mechanism study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and explore efficacy of GSK2330811 in participants with diffuse cutaneous systemic sclerosis.

Protocol Number: 201247/05

Short Title: Proof of mechanism study of GSK2330811 in diffuse cutaneous systemic sclerosis.

Compound Number: GSK2330811

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): P-IND 131823 and EudraCT number 2016-003417-95

Approval Date: 01-APR-2020

From: Nicolas Wisniacki
To: PPD
Cc: PPD
Subject: Re: 201247 Amendment #5 for Sponsor Sign-off
Date: Wednesday, April 01, 2020 1:56:08 PM
Attachments: image002.png

Approved.

Nic

From: PPD
Sent: Wednesday, April 1, 2020 6:37:28 PM
To: Nicolas Wisniacki PPD
Cc: PPD
Subject: 201247 Amendment #5 for Sponsor Sign-off

Hi Nic,

Attached please find the post-compliance checked amendment for your review and approval.

Document Description: Protocol amendment #5

Document #: 2016N269831_05

Protocol Title: A multi-centre, randomized, double-blind (sponsor open), placebo-controlled, repeat-dose, proof of mechanism study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and explore efficacy of GSK2330811 in participants with diffuse cutaneous systemic sclerosis.

Protocol Number: 201247/05

Overall Rationale for the Amendment: This amendment was executed to provide clarification on the points detailed below:

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities 9 Study Assessments and Procedures	Updated to allow a virtual or telephone visit at Day 113, Day 155, Day 197 and Early Withdrawal (if required) to perform any study assessments that can be conducted remotely in circumstances in which an on-site visit is not possible due to the COVID-19 pandemic.	At the time of this amendment, all study participants have completed the treatment period. In response to the COVID-19 pandemic, the option of virtual/telephone visits added to ensure safety monitoring during the off-treatment follow-up period.

2 Schedule of Activities	Updated to extend the visit window on Day 113 to ± 5 days, and on Day 155 and Day 197 to ± 10 days.	At the time of this amendment, all study participants have completed the treatment period. In response to the COVID-19 pandemic, the visit window has been extended to provide flexibility to ensure safety monitoring during the off-treatment follow-up period.
2 Schedule of Activities 12.2 Appendix 2: Clinical Laboratory Tests	Updated to allow safety (hematology and chemistry) labs and pregnancy tests to be run locally at the clinical site or within the community at the discretion of the Investigator for the Day 113, Day 155, Day 197 and Early Withdrawal (if required) visits. Updated to allow urine pregnancy test to be performed for the Day 197 and Early Withdrawal (if required) visits if a serum pregnancy test can not be performed.	At the time of this amendment, all study participants have completed the treatment period. In response to the COVID-19 pandemic, local safety labs and pregnancy tests can be run to ensure safety monitoring during the off-treatment follow-up period.

If you approve, can you please provide approval **via email response,** which is deemed an acceptable workaround at this time to the wet-ink process, per recent guidance. I will file this email in TMF to document Sponsor approval for this amendment.

Thank you!

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	01-Apr-2020
Amendment 4	12-Nov-2018
Amendment 3	20-Jul-2017
Amendment 2	12-Dec-2016
Amendment 1	01-Nov-2016
Original Protocol	13-Sep-2016

Amendment 5 01-Apr-2020

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1. SYNOPSIS

Protocol Title: A multi-centre, randomized, double-blind (sponsor open), placebo-controlled, repeat-dose, proof of mechanism study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and explore efficacy of GSK2330811 in participants with diffuse cutaneous systemic sclerosis.

Short Title: Proof of mechanism study of GSK2330811 in diffuse cutaneous systemic sclerosis.

Rationale: Systemic sclerosis (SSc) is a rare autoimmune disease with high morbidity and mortality. There are no approved disease-modifying therapies and it is an area of high unmet medical need. GSK2330811 is a monoclonal antibody that binds and neutralises Oncostatin M (OSM). The biological roles of OSM indicate that blocking OSM signalling would be expected to inhibit the key pathologic processes of SSc. This is a proof of mechanism study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of repeat subcutaneous doses of GSK2330811 in participants with diffuse cutaneous SSc (dcSSc).

Objectives and Endpoints:

Objective	Endpoint
Primary • To evaluate the safety and tolerability of repeat subcutaneous doses of GSK2330811 in participants with dcSSc	• Adverse event reporting • Laboratory safety data (clinical chemistry, haematology, urinalysis) • Vital signs (blood pressure, heart rate, body temperature) • 12 lead ECGs
Secondary • To evaluate the pharmacokinetic profile of repeat subcutaneous doses of GSK2330811 in participants with dcSSc	• Plasma concentrations of GSK2330811 and derived pharmacokinetic parameters (e.g Ctrough, apparent clearance (CL/F) and apparent volume of distribution (Vss/F))
• To assess the target engagement of repeat subcutaneous doses of GSK2330811 in the blood of participants with dcSSc	• Serum levels of total OSM • Serum levels of free OSM

Objective	Endpoint
• To assess the potential for anti-drug antibody formation following repeat subcutaneous doses of GSK2330811 in participants with dcSSc	• Incidence and titres of anti-GSK2330811 antibodies

Additional exploratory endpoints are included to explore the pharmacology of repeat subcutaneous doses of GSK2330811 and its effect on selected clinical endpoints and biomarkers of fibrosis, inflammation and vasculopathy in the blood and skin.

Overall Design: This is a multi-centre, randomised, double-blind (sponsor open) placebo controlled, repeat-dose, proof of mechanism study of subcutaneous administration of GSK2330811 in males and females with dcSSc.

Participants with active disease and a disease duration of ≤60 months will be enrolled. Mycophenolate and low dose corticosteroids are permitted as background therapies.

The study includes two sequential cohorts. Cohort 1 will evaluate the safety and tolerability of a repeat-dose predicted to provide sub-maximal inhibition of OSM, leading to a dose escalation decision. Cohort 2 will then evaluate a repeat-dose predicted to provide maximal inhibition of OSM to test proof of mechanism. A Data Review Committee will be responsible for determining progression from cohort 1 to cohort 2.

Participants will be randomised in a 3:1 ratio within each cohort to GSK2330811 and placebo respectively.

Assessments performed during the study will include skin biopsies, home spirometry (forced vital capacity) and an optional skin suction blister procedure for participants in cohort 2.

Number of Participants: A minimum of approximately 24 participants and a maximum of 40 participants will be randomised across the two cohorts.

Treatment Groups and Duration: Participants in both cohorts will be dosed subcutaneously for 10 weeks (total of 6 doses) with either GSK2330811 or placebo. Cohort 1 will receive 100 mg GSK2330811 or placebo every other week and cohort 2 will receive 300 mg GSK2330811 or placebo every other week.

The duration of the study for the participants will be up to 34 weeks including a screening period of up to 6 weeks, a treatment period of 12 weeks and a follow-up period of 16 weeks.

2. SCHEDULE OF ACTIVITIES (SOA)

The timing and number of planned pharmacokinetic, target engagement and biomarker 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 these assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files.

- **Screening**

Procedure	Screening (between -42 and -1 days)	Notes
Informed Consent	X	**The screening period for women of child bearing potential (WOCBP) must be at least 28 days to allow for a 28 day interval between the screening and Day 1 pregnancy tests.** See Appendix 1 for abbreviations. 1. Respiratory laboratory FVC will be used for study eligibility and will be entered into the eCRF. 2. The participant will be trained in FVC measurement using a hand held device. The first set of triplicate readings will be recorded by the participant at the clinical site. Thereafter approximately weekly measurements will be collected by the participant and entered into a paper diary. 3. QuantiFERON-TB Gold PLUS test is also acceptable.
Inclusion and Exclusion Criteria	X	
Demographics	X	
Complete Physical Exam	X	
Medical History	X	
mRSS	X	
Respiratory Laboratory FVC[1]	X	
Home spirometry FVC[2]	X	
DLCO - corrected for haemoglobin	X	
Concomitant Medications	X	
12 lead ECG - single measurement	X	
Vital Signs (blood pressure, heart rate, body temperature)	X	
QuantiFERON-TB Gold test[3]	X	
Serum Pregnancy Test (WOCBP only)	X	
Oestradiol + FSH (as needed see Appendix 2)	X	
HIV, Hepatitis B and Hepatitis C	X	
Standard Haematology / Clinical Chemistry / Urinalysis (listed in Appendix 2)	X	
Additional Haematology (listed in Appendix 2)	X	
CRP	X	
SAE - commencing from time of informed consent	X	

- **Treatment Days and Follow-Up**

Procedure	Treatment Period (Days)										
	Day 1	Day 15 ± 2 days	Day 29 ± 2 days	Day 43 ± 2 days	Day 57 ± 2 days	Day 71 ± 3 days	Day 85 ± 3 days	Day 113 ± 5 days	Day 155 ± 10 days	Day 197 ± 10 days (Final Follow –Up)	Early Withdrawal[13] (refer Section 8.2)
Study Week		W2	W4	W6	W8	W10	W12	W16[13]	W22[13]	W28[13]	
Study Treatment											
Randomisation	X[1]										
Study Treatment Administration	X	X	X	X	X	X					
Baseline Assessments											
Autoantibodies	X[1]										
Medical History[2]	X[1]										
Safety Assessments and Cardiac Monitoring											
Complete Physical Exam	X[1]									X	X
Brief Physical Exam		X	X	X	X	X	X	X	X		
Vital Signs (blood pressure, heart rate, temperature)	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X	X
12 –lead ECG (triplicate at day 1 or if QTc abnormal)	X[1]	X[1]			X[1]						
AE/SAE Review[3, 13]	Continuous throughout study										
Concomitant Medication Review[13]	Continuous throughout study										
Serum Pregnancy Test (WOCBP)[13]										X[14]	X[14]
Urine Pregnancy Test (WOCBP)[13]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X		
Standard Haematology/Clinical Chemistry (see Appendix 2)[13]	X[1, 4]	X	X	X	X	X	X[4]	X	X	X	X

Procedure	Treatment Period (Days)										
	Day 1	Day 15 ± 2 days	Day 29 ± 2 days	Day 43 ± 2 days	Day 57 ± 2 days	Day 71 ± 3 days	Day 85 ± 3 days	Day 113 ± 5 days	Day 155 ± 10 days	Day 197 ± 10 days (Final Follow –Up)	Early Withdrawal[13] (refer Section 8.2)
Study Week		W2	W4	W6	W8	W10	W12	W16[13]	W22[13]	W28[13]	
Additional Haematology (see Appendix 2 for list)	X[1]						X			X	X
Urinalysis	X[1]						X			X	X
Pharmacokinetics, Pharmacodynamics, Immunogenicity and Genetics											
Optional Suction Blister[5]					←--------X--------→						
Immunogenicity Sampling	X[1]	X			X		X			X	X
Pharmacokinetic Blood Sampling	X[1]	X	X		X		X	X	X	X	X
Target Engagement (OSM) Blood Sampling	X[1]	X	X		X		X	X	X	X	X
Genetic Sampling[6]	X										
Disease markers (efficacy) Assessment											
Skin Biopsy	X[1]						X[7]				X[8]
Blood Biomarkers (see Section 9.8.1)	X[1,9]		X		X		X[9]			X	
C-reactive protein (CRP)	X[1]	X	X		X		X	X		X	X
mRSS	X[1]				X		X			X	X[10]
Respiratory Laboratory FVC	X[1]						X			X	X[10]
Home Spirometry FVC[11]	<----------weekly---------->										
SHAQ /PhGA//PtGA/CRISS data[12]	X[1]						X			X	

1. To be performed pre-dose.
2. Medical history will include smoking history and information regarding the participant's most recent HRCT scan if available. Medical occurrences that begin before the start of study treatment (Day 1) but after obtaining informed consent will be recorded as medical history.
3. SAEs will be recorded from signing of informed consent; AEs will be recorded from administration of first study treatment.
4. Day 1 predose sample and Day 85 (Week 12) will be fasted and include lipid assessments.
5. Suction blister is an optional procedure for cohort 2 and additional consent will be required. Suction blister will only be performed once per participant (at anytime from the Day 57 (Week 8) visit to the Day 85 (Week 12) visit inclusive) at selected sites
6. Genetics sampling is an optional assessment and additional consent will be required. Genetic sample can be taken any time after randomisation.
7. Skin biopsy scheduled for Day 85 (Week 12) may be taken on an alternative day to the rest of the assessments, but must remain within the Day 85 (Week 12 $\pm$ 3 days) time window.
8. Skin biopsy only performed if the early withdrawal visit occurs on or after the Day 57 (Week 8) visit but before when the Day 85 (Week 12) visit would have been scheduled and the participant is willing.
9. At the Day 1 and Day 85 (Week 12) visits, additional blood volume is required for possible proteomic and transcriptomic analyses.
10. Respiratory Laboratory FVC and mRSS will only be performed if the early withdrawal visit occurs on or after the Day 57 (Week 8) visit.
11. Home spirometry FVC measured weekly by the participant via a hand held device, until the Day 197 (Week 28) visit.
12. Data to support CRISS calculation will be collected at Day 1, Day 85 (Week 12) and Day 197 (Week 28).
13. If an on-site visit is not possible due to the COVID-19 pandemic, a virtual or telephone visit can be performed for any study assessments that can be conducted remotely (e.g., AE/SAE review & concomitant medication review). In these circumstances, scheduled safety (standard hematology and clinical chemistry) labs and pregnancy tests should be performed if feasible and may be performed locally at the clinical site or within the community (all at the discretion of the Investigator).
14. If it is not possible for a serum pregnancy test to be performed due to the COVID-19 pandemic, a urine pregnancy test should be performed if possible.

3. INTRODUCTION

3.1. Study Rationale

Systemic sclerosis (SSc) is a rare autoimmume disease with high morbidity and mortality. There are no approved disease modifying therapies and it is an area of high unmet medical need. This is a proof of mechanism (POM) study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of repeat subcutaneous (SC) doses of GSK2330811 in participants with diffuse cutaneous systemic sclerosis (dcSSc).

This is the first study with GSK2330811 in participants with SSc and as such the primary objective is to assess the safety and tolerability of repeat-doses of GSK2330811. Secondary and exploratory objectives include an assessment of the PK profile and immunogenicity of GSK2330811 with repeat-doses and proof of target engagement and pharmacology in blood and skin.

Mechanistic biomarkers of fibrosis, inflammation and vasculopathy will be measured in blood and skin in order to provide evidence of the modulation of key biological pathways involved in the pathogenesis of SSc by GSK2330811. Clinical data on the extent of skin and lung involvement by disease will be collected in order to provide further understanding of the mechanism of action and potential for clinical efficacy of GSK2330811 in SSc. However due to the small size and short duration of the study, no formal hypothesis will be tested.

3.2. Background

GSK2330811 is a humanised immunoglobulin G1κ (IgG1κ) monoclonal antibody that binds and neutralises Oncostatin M (OSM) with high affinity and specificity. This inhibits the downstream actions of OSM, which include effects on fibroblasts, endothelial cells and leukocytes that have been associated with fibrosis, vasculopathy and inflammation in a number of diseases.

OSM is a member of a family of secreted cytokines that also includes interleukin 6, leukemia inhibitory factor (LIF) and interleukin 31. It is produced by leukocytes, including macrophages, activated T cells and neutrophils and acts primarily via OSM receptors (OSMR) on a broad range of cell types, including chondrocytes, fibroblasts, keratinocytes and endothelial cells [Gearing, 1992; Mosley, 1996] to elicit diverse biological functions [Hermanns, 2015]. Depending on context, OSM is capable of endothelial activation; inducing an acute phase response; inducing cellular proliferation, migration or differentiation (e.g. of fibroblasts, epithelial cells and keratinocytes); inducing the release of inflammatory mediators and promoting wound healing [Richards, 2013; Modur, 1997]. OSM also has a secondary role in regulating erythropoesis and megakaryopoesis [Tanaka, 2003; Minehata, 2006]. In a mouse model, intranasal OSM was able to induce lung fibrosis accompanied by significant increases in alveolar macrophages, lymphocytes and neutrophils [Mozaffarian, 2008].

SSc is a multisystem autoimmune disease, in which the interrelated processes of inflammation, fibrosis and microvascular damage result in a complex pattern of organ-based complications with high mortality and morbidity [Allanore, 2015]. There are no approved drugs for the treatment of SSc and as such it remains an area of great unmet medical need [Denton, 2013]. Given the concordance between the known biological roles of OSM and the key pathologic processes in SSc (i.e. inflammation, microvascular damage and fibrosis), inhibiting OSM signalling in patients with SSc has potential to slow or stop the disease process thereby providing a disease-modifying therapeutic benefit. This is further supported by elevated serum levels of OSM in SSc patients compared to healthy controls, by elevated OSM levels in bronchoalveolar fluid of SSc patients with alveolitis and by increased tissue expression of OSM and OSMR in involved skin of SSc patients by immunohistochemistry [Feeney, 2015; Mozaffarian, 2008].

The safety profile of GSK2330811 was evaluated in a repeat-dose subcutaneous toxicity study in the cynomolgus monkey. The only observed findings were reduction in red cell parameters in peripheral blood and bone marrow with evidence of a regenerative reticulocyte response. The no observed adverse effect level (NOAEL) was considered to be 300 mg/kg (highest dose tested). Detailed information can be found in the Investigator's Brochure (IB) for GSK2330811 [GlaxoSmithKline Document Number 2016N284919_00].

There has been one study of GSK2330811 in humans to date. In a Phase I, single dose escalation study in healthy males and females of non-childbearing potential, 30 participants were exposed to GSK2330811 at doses ranging from 0.1 mg/kg to 6.0 mg/kg. GSK2330811 was well-tolerated, with no deaths or other 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 dose-dependent, 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 6 mg/kg dose level. These effects are both felt to relate to inhibition of the known actions of OSM by GSK2330811. Detailed information can be found in the IB for GSK2330811 [GlaxoSmithKline Document Number 2016N284919_00].

3.3. Benefit/Risk Assessment

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2330811]		
Haematological Thrombocytopaenia Anaemia	• OSM has been shown to modulate haematopoiesis through an effect on bone marrow stromal cells and haematopoietic progenitors [Wallace, 1995; Miyajima, 2000]. • OSM also positively influences the maturation of megakaryocytes and affects the expression of other cytokines in the bone marrow stroma, which regulate the bone marrow microenvironment [Tanaka, 2003]. • A FTIH study of single doses of GSK2330811 in healthy participants demonstrated a reversible reduction in platelet count at doses between 1 mg/kg and 6 mg/kg and on red cell parameters including haemoglobin and red cell count at the highest dose level of 6 mg/kg. A rebound 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_00]. • A 3 month repeat-dose cynomolgus monkey toxicology study with GSK2330811 showed a reduction in red cell parameters and bone marrow myeloid to erythroid ratios with a compensatory increase in reticulocyte count, without clinical	• Only participants with Haemoglobin ≥110g/L and platelet count ≥150x10^9/L at screening, will be included in the study. • Participants with known bleeding or coagulation disorders will be excluded. • Participants receiving treatment with anti-coagulant medications will be excluded. • Participants receiving treatment with anti-platelet medications, other than aspirin or non-steroidal anti-inflammatory drugs, will be excluded. • Red cell and platelet parameters will be tested every two weeks during the treatment period (from the Day 1 to the Day 85 (Week 12) visit and then at each scheduled visit until the end of the follow-up period to ensure careful monitoring. • Dosing of an individual participant will cease if haemoglobin <80g/L or platelet count <50x10^9/L with additional testing prior to dosing, if necessary (see Section 8.1.4). • Dosing of an individual participant will be held if platelet count between 50x10^9/L and 75x10^9/L (see Section 8.1.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	correlates. There was partial to complete recovery of red cell parameters and reticulocytes at the end of the off drug phase (18 weeks). Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_00]. • A marginal decrease in platelet count (platelet counts remained within the reference range) was also observed in the same 3 month toxicology study. These showed partial to complete recovery whilst administration of GSK2330811 was ongoing and full recovery at the end of the off drug period (18 weeks). Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_00].	• The effect of a submaximal dose of GSK2330811 on haematologic parameters will be evaluated in an initial safety cohort (cohort 1) before a decision is made to enrol participants into the higher dose cohort (cohort 2). • Study safety monitoring will include in-stream monitoring of haemoglobin and platelet counts and planned safety reviews will be conducted after 4, 8, 12 participants in cohort 2 (see Appendix 3).
Risk of infection (including of reactivation of Mycobacterium tuberculosis)	• OSM contributes to immunity in synergy with other cytokines such as TNF and IL-1 [Barksby, 2006], 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. • 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. • In cynomolgus monkey toxicology studies of GSK315234, another IgG anti-OSM monoclonal antibody with similar affinity for cynomolgus OSM, no changes in the adaptive immune response (T cell dependent B cell response), white cell count, or	• Participants to be screened for Human Immunodeficiency virus (HIV), Hepatitis B Hepatitis C and latent Tuberculosis prior to enrolment and excluded if positive. • Participants with a history of opportunistic infections within 6 months of the Day 1 visit or recurrent infection, as determined by the investigator, will be excluded. • Participants with a history of serious infection requiring intravenous (IV) antibiotics and/or hospitalisation within 3 months prior to the Day 1 visit will be excluded. • Participants that have taken oral antibiotics, for the treatment of an acute or chronic infection, within 4 weeks prior to the Day 1 visit. • Participants with active or unresolved infection,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	leukocyte subpopulations including T lymphocyte subsets were noted. • No specific studies have been conducted in nonclinical species to investigate the effect of GSK2330811 on the response to viral or bacterial infection.	including osteomyelitis, at the Day 1 visit will be excluded. • Investigators are expected to assess participants' vaccination status and to follow local and/or national guidelines with respect to vaccinations. • Participants will not be allowed to receive live vaccines within the 4 weeks prior to Day 1, until the end of follow-up. • Close monitoring of participants for infections: Investigators will be made aware of the importance of reporting infections. Participants will be asked specifically regarding signs and symptoms of infection. White cell count and differential and vital signs will be obtained at each study visit. In the event of a serious infection, study treatment will be discontinued.
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. Treatment unrelated pre-existing antibodies were detected in 3 participants at baseline including in one participant receiving placebo. These were low titre and not associated with any specific AEs.	• The risk of developing ADA and their clinical consequences are mitigated as GSK2330811 is a fully humanized monoclonal antibody. Fully human antibodies are less immunogenic than their murine or chimeric monoclonal counterparts [Schroff, 1985; Shawler, 1985]. • Serum samples will be collected for detection of ADA at timepoints aligned with regulatory guidelines [EMA, 2010; FDA, 2009].

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. Administration of OSM ameliorated liver injury in wild-type mice [Nakamura, 2004]. • However, in a 3 month toxicity study in healthy cynomolgus monkeys, treatment with GSK2330811 was not associated with any observed liver effects (no changes in liver weights, macroscopic or microscopic changes, or elevations in liver transaminases at doses up to and including 300 mg/kg/week). Refer to IB for details [GlaxoSmithKline Document Number 2016N284919_00]. • Mild, isolated, transient elevations in ALT, AST and serum 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_00].	• Participants will be screened for Hepatitis C and Hepatitis B prior to enrolment and excluded if positive. • Participants with a current or chronic history of liver disease or a history of alcohol misuse will be excluded. • Only participants with an acceptable ALT and serum bilirubin at screening will be included, as detailed in the exclusion criteria. • Standard GSK guidance for phase 2 studies on liver monitoring and on liver stopping rules as detailed in Appendix 7 and Section 8.1.2 , will be followed for all participants.
Reproductive Toxicity	• Animal reproductive toxicity studies have not yet been carried out with GSK2330811. They will be conducted in accordance with current ICH guidelines for timings. • Animal reproductive toxicity studies have been carried out for GSK315234, another IgG anti-OSM monoclonal antibody. GSK2330811 and GSK315234 antibodies bind different epitopes but	• Pregnant and lactating females will be excluded. • Women of child bearing potential (WOCBP) are required to use highly effective methods of contraception, as detailed in Appendix 5, from 28 days prior to the first dosing day (Day 1) until the final follow-up visit. • WOCBP will undergo pregnancy testing at screening, prior to each study treatment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have similar affinity for OSM in the animal model used. No GSK315234 related effects on pregnancy, embryofetal 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.	administration and at all other study visits. A minimum of 28 days between the screening pregnancy test and the Day 1 pregnancy test is required for WOCBP. • In the event of a pregnancy in a female participant, study treatment will be discontinued and information on the pregnancy will be collected as detailed in Appendix 5.
Carcinogenicity	• There is conflicting evidence for the role of OSM in cell proliferation in metastatic cancer. Data is 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 the exception of basal cell carcinoma that has been completely excised prior to the study. • Adverse event monitoring.
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 sensitivity to any of the study treatments, or a history of any drug or other allergy that in the opinion of the investigator precludes their participation, will be excluded. • Administration of GSK2330811 will be conducted in a hospital setting, with appropriate medical intervention available. • Participants will be informed of the symptoms of systemic hypersensitivity reactions and be instructed to seek immediate clinical care should they occur. This information will also be contained within the informed consent form.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Skin Biopsy	• Skin biopsy is a well-established procedure implemented in a number of clinical studies in SSc patients [Guo, 2015; Khanna, 2016; Rice, 2015]. • Possible risks of this procedure may include discomfort during and after the biopsy skin punch, infection and bleeding. • OSM and OSMR are expressed in the epidermis and may play a role in wound healing (Duncan, 1995; Ihn, 2000; Scaffidi, 2002; Canady, 2013). However, there were no adverse events related to blister healing reported in the FTIH study with GSK2330811.	• Participants must have no contraindications that, in the opinion of the investigator, would preclude skin biopsy. • Participants receiving treatment with anti-coagulant medications will be excluded. • The biopsy procedure will be performed according to local practice, by trained personnel using aseptic technique to reduce the risk of bleeding and scarring. • Participants will be instructed on the signs and symptoms of infection and to contact site personnel should these develop. • The number of biopsies obtained will be limited to four, the minimum number necessary to answer the study questions.
Skin Suction Blister	• The skin suction blister technique has been performed previously on patients with SSc [Clark, 2015]. • Possible risks of this procedure may include discomfort during the application of the negative pressure, skin infection after drawing the blister and hyperpigmentation of the skin at the blister induction site. • OSM and OSMR are expressed in the epidermis, and may play a role in wound healing Duncan, 1995; Ihn, 2000; Scaffidi, 2002; Canady, 2013].	• Participants must have no contraindications that, in the opinion of the investigator, would preclude a skin suction blister. • Participants receiving treatment with anti-coagulant medications will be excluded. • The risk of infection, although minimal given the low invasiveness of the procedure, will be reduced by dressing the blister after drawing the fluid. Participants will be advised to keep the site covered and dry for 24 hours before leaving open to the air.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Skin suction blisters were well tolerated in the FTIH study with GSK2330811 and no adverse events related to blister healing were reported.	• Skin blister healing will be monitored during the study as part of adverse event (AE) review. • Participants will be instructed on the signs and symptoms of infection, and to contact site personnel should these develop.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2330811 may be found in the IB for GSK2330811 [GlaxoSmithKline Document Number 2016N284919_00].

3.3.2. Benefit Assessment

Systemic sclerosis is an autoimmune disease with substantial excess morbidity and mortality, and for which no licensed disease modifying treatments are available. There is pre-clinical evidence to suggest that GSK2330811 may be effective in treating the underlying disease process and therefore in ameliorating the signs and symptoms of SSc in an individual participant receiving GSK2330811. However, should there be any direct benefit to a participant in the study, this may be limited by the short duration of treatment in an otherwise chronic disease.

3.3.3. Overall Benefit:Risk Conclusion

Balanced against the measures taken to minimise them, the potential haematologic and other risks to participants in this POM study of GSK2330811 are justified by need to develop more effective treatments for SSc.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the safety and tolerability of repeat subcutaneous doses of GSK2330811 in participants with dcSSc	• Adverse event reporting • Laboratory safety data (clinical chemistry, haematology, urinalysis) • Vital signs (blood pressure, heart rate, body temperature) • 12 lead ECGs
Secondary • To evaluate the pharmacokinetic profile of repeat subcutaneous doses of GSK2330811 in participants with dcSSc	• Plasma concentrations of GSK2330811 and derived pharmacokinetic parameters (e.g Ctrough, apparent clearance (CL/F) and apparent volume of distribution (Vss/F))
• To assess the target engagement of repeat subcutaneous doses of GSK2330811 in the blood of participants with dcSSc	• Serum levels of total OSM • Serum levels of free OSM
• To assess the potential for anti-drug antibody formation following repeat subcutaneous doses of GSK2330811 in participants with dcSSc	• Incidence and titres of anti-GSK2330811 antibodies

Objectives	Endpoints
Exploratory • To explore the pharmacology of repeat subcutaneous doses of GSK2330811 and its effects on biomarkers of fibrosis, inflammation and vasculopathy in the blood and skin of participants with dcSSc	• Endpoints may include (but are not limited to): ○ Skin Biopsies: Change from baseline in mRNA expression and protein levels of selected markers chosen to reflect fibrosis, vasculopathy and tissue inflammation (e.g. αSMA, CD31 and CD3 respectively) at Day 85 (Week 12) ○ Blood: Change from baseline over time in CRP, other soluble protein markers (e.g. collagen turnover, VEGF and IL-6) and mRNA expression
• To explore the PK and target engagement of repeat subcutaneous doses of GSK2330811 in the skin of participants with dcSSc using suction induced blisters	• Endpoints may include (but are not limited to): ○ Levels of GSK2330811 in blister fluid measured anytime between Day 57 and Day 85 (Week 8 and Week 12) ○ Levels of OSM in blister fluid measured anytime between Day 57 and Day 85 (Week 8 and Week 12)
• To explore the effect of repeat subcutaneous doses of GSK2330811 on the extent of skin involvement in participants with dcSSc	• Change from baseline in modified Rodnan skin score (mRSS) over time
• To explore the effect of repeat subcutaneous doses of GSK2330811 on lung function in participants with dcSSc	• Rate of change in forced vital capacity (FVC) • Change from baseline in FVC
• To explore the effect of repeat subcutaneous doses of GSK2330811 on SSc related symptoms, physical function and disease activity in participants with dcSSc	• Change from baseline in Scleroderma Health Assessment Questionnaire (SHAQ) • Change from baseline in Physician Global Assessment of Disease Activity (PhGA) • Change from baseline in Patient Global Assessment of Disease Activity (PtGA) • Composite Response Index for Systemic Sclerosis (CRISS)

Objectives	Endpoints
• To characterise the mechanisms of any observed haematological effects of GSK2330811.	• Change from baseline in selected blood markers related to mechanisms of anaemia and thrombocytopenia.

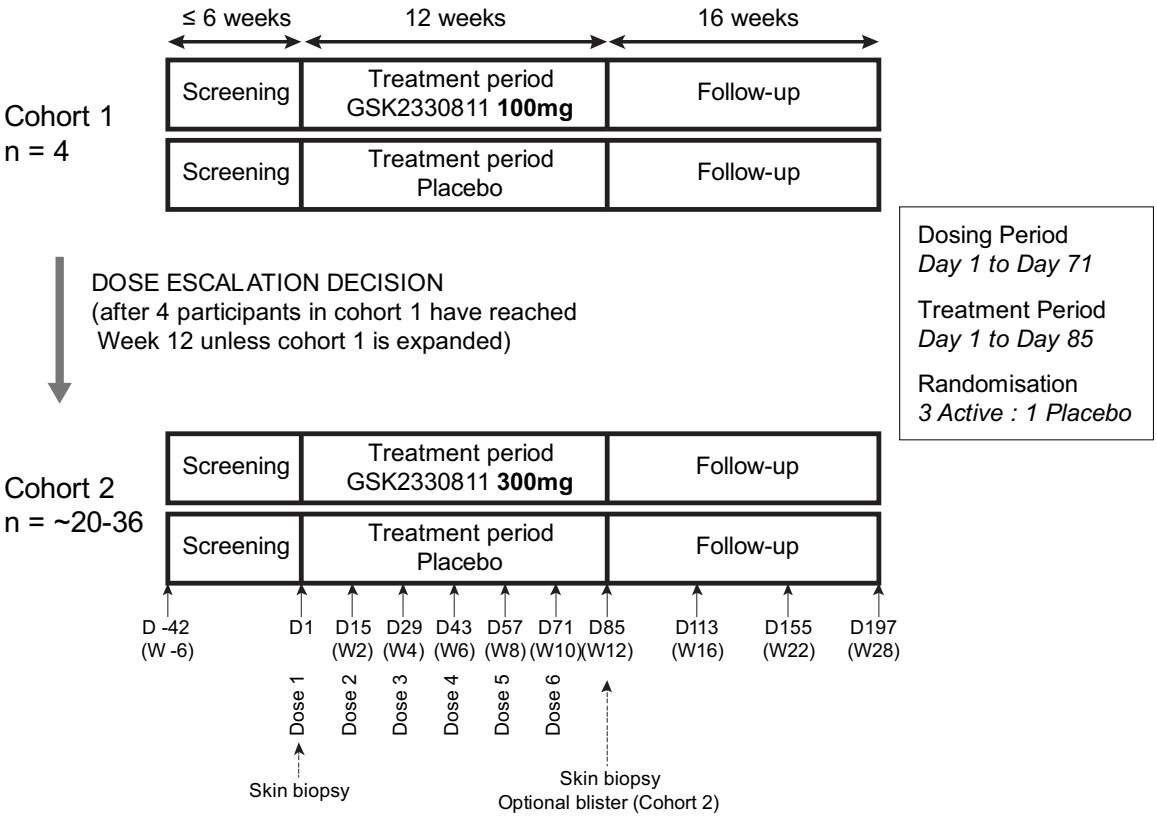
5. STUDY DESIGN

5.1. Overall Design

This is a multi-centre, randomised, double blind (sponsor open), placebo-controlled, repeat-dose, proof of mechanism study of subcutaneous administrations of GSK2330811 in males and females with dcSSc.

The study includes two sequential cohorts. Cohort 1 is planned to consist of at least 4 participants and will evaluate a repeat-dose predicted to provide sub-maximal inhibition of OSM, leading to a dose escalation decision once at least 4 participants have reached the end of the treatment period (see Section 7.2). Cohort 2 will then evaluate a repeat-dose, predicted to provide maximal inhibition of OSM, to test POM. The study design, for both cohorts, is depicted in Figure 1.

Figure 1 Study Schematic



- Participants who consent will attend the clinical facility for screening and if eligible will enter the treatment period of the study within 42 days.
- The screening period will be at least 28 days for WOCBP to allow for a minimum 28 day interval between the screening and Day 1 pregnancy tests.
- Participants will be randomised in a 3:1 ratio within each cohort to GSK2330811 and placebo respectively. In cohort 2 treatment allocation will be stratified according to mycophenolate concomitant medication status (treated or non-treated).
- Participants will attend the clinical facility to receive a subcutaneous dose of GSK2330811 or placebo on Day 1 and then every other week until the sixth and final dose at the Day 71 (Week 10) visit.
- A Data Review Committee (DRC) will be responsible for determining progression from cohort 1 to cohort 2 as described in Section 7.2.
- Interim analyses will be conducted during cohort 2. The rationale, conduct and potential outcomes of these are described in Section 10.3.3.
- Study safety monitoring will be undertaken in a blinded manner by the Sponsor Safety Review Team (SRT) as described in Appendix 3. The Study Medical Monitor will also continuously review adverse events and laboratory tests for individual participants during the conduct of the study to ensure individual participant monitoring.
- Skin biopsies will be collected to assess GSK2330811 pharmacology and biomarkers at the site of action. Two punch biopsies will be collected from involved skin, on the forearm of participants, on both Day 1 and during the Day 85 (Week 12) visit window.
- A skin suction blister procedure will be performed on involved skin on the forearm of participants at selected sites at anytime between the Day 57 (Week 8) visit and the Day 85 (Week 12) visit inclusive. This will be optional for participants and only performed in participants enrolled in cohort 2.
- After the treatment period, participants will enter a follow-up period of approximately 16 weeks.
- In addition to study visits, weekly home FVC monitoring will be undertaken during the study (from screening until Day 197 (Week 28)).

5.2. Number of Participants, Treatment Arms and Duration

Participants with dcSSc, with active disease and a disease duration of ≤ 60 months, will be enrolled. A minimum of approximately 24 participants and a maximum of 40 participants will be randomised across two cohorts. The duration of the study, including screening, will be up to 34 weeks for participants.

Participants will be dosed subcutaneously at one of two dose levels every other week for 10 weeks with either GSK2330811 or placebo.

For cohort 1, an initial 4 participants will be randomised to either GSK2330811 or placebo. If a decision is made to expand cohort 1 a further 4 participants will be entered into cohort 1. For cohort 2, a minimum of approximately 20 participants will be randomised. Participants from Cohort 1 will not be eligible to participate in Cohort 2.

A participant in cohort 1 is evaluable for dose escalation if they have received at least 4 doses of GSK2330811 or placebo, have reached the end of the treatment period and there is a standard haematology result from at least one of the Day 71 (Week 10), Day 85 (Week 12) or Day113 (Week 16) visits. If any participant in cohort 1 cannot be evaluated for dose escalation, additional participants may be recruited and assigned to the same treatment sequence at the discretion of the sponsor up to a maximum of 8 evaluable participants.

A participant in cohort 1 or cohort 2 is considered evaluable for study endpoints if they have received at least 4 doses of GSK2330811 or placebo and have biopsies at both the Day 1 and the Day 85 (Week 12) assessment. Additional participants may be entered into the study at the discretion of the sponsor up to a maximum of 40 randomised participants in the study overall.

5.3. Participant and Study Completion

Participants will complete the study once they have completed all assessments on Day 197 (Week 28). This includes participants who discontinue study treatment early but continue in the study.

Participants who withdraw from the study early will complete the study once they have completed all assessments at the early withdrawal visit (Section 8.2).

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

5.4. Scientific Rationale for Study Design

As this is the first study of GSK2330811 in participants with SSc, and the first repeat dose study, the primary endpoint is the safety and tolerability of GSK2330811. In addition, this study will include assessments of the pharmacokinetics, target engagement and downstream pharmacology of GSK2330811. This will be achieved by assessing GSK2330811 and OSM levels in blood and skin blister fluid and mRNA markers of GSK2330811 pharmacology in skin biopsies. Skin involvement is emphasised because it is readily studied, contributes substantially to the morbidity experienced by patients with dcSSc and exemplifies the three major pathological processes involved in the condition.

The assessment of biomarkers of fibrosis, inflammation and vasculopathy in blood and skin biopsies will also be performed, and for this reason the population is enriched for early active disease. Changes in these parameters and their association with each other and with preliminary measures of clinical efficacy will be assessed. These data are intended to provide evidence that GSK2330811 is having an impact on key pathways involved in the pathogenesis of SSc.

The purpose of cohort 1 is to evaluate the safety and tolerability of repeat doses of a pharmacologically active but submaximal dose of GSK2330811, before escalating to a higher dose.

The 12 week duration of the Treatment Phase is based on the expectation that an effective therapy should cause changes in the mechanistic parameters at this timepoint [Guo, 2015; Khanna, 2016; Rice, 2015].

The GSK2330811 half life is between 19 to 25 days, consistent with a typical monoclonal antibody half life for a soluble cytokine (see IB for GSK2330811) [GlaxoSmithKline Document Number 2016N284919_00]. Participants will be followed for approximately 18 weeks after the last administration of GSK2330811.

The placebo group is required for a valid evaluation of adverse events attributable to GSK2330811 treatment versus those independent of GSK2330811 treatment. The placebo participants will also serve as negative controls for the biomarker and efficacy assessments.

Participants will be randomised in a 3:1 ratio to GSK2330811 and placebo respectively. This unbalanced allocation ratio means that more participants are available for the assessment of within-participant changes in biomarkers after dosing with GSK2330811 and allows more participants to receive GSK2330811.

Participants will be allowed to continue with some background therapies (Section 7.7), including mycophenolate and low dose oral corticosteroids to avoid excluding potential participants in this rare disease. Other immunosuppressive treatments will be excluded, in order to minimise inter-participant variability in this small trial.

5.5. Dose Justification

Dose levels for this study have been selected on the basis of PK/PD predictions, data from the first time in human study with GSK2330811 and preclinical data. Two dose levels (a 100 mg sub-maximal dose to test initial safety and tolerability and a 300 mg maximal dose to test POM) have been selected based on predicted target engagement after repeat dosing.

An in-vivo affinity of approximately 0.6 nM was estimated from first time in human data. The typical GSK2330811 apparent distribution volume was 11.5 L (95% Confidence Interval (CI): 10.2-13.1) and the typical apparent systemic clearance was 14.1 mL/hr (95% CI: 12.7-15.6). The mean terminal half-life ranged between 19 and 25 days. The ratio of GSK2330811 mean concentration between skin blister fluid and plasma ranged from 19 to 45%.

A target-mediated drug disposition (TMDD) model (Mager, 2005) using a one-compartment PK model together with binding kinetics of drug and target was developed to predict target engagement after repeat dosing.

First cohort: 100 mg every other week is considered a sub-maximal pharmacologically active dose with a predicted target engagement of approximately 80% in serum at trough.

Second cohort: 300 mg is predicted to achieve engagement of greater than 90% of OSM in serum at trough.

In addition a PKPD model was developed to assess the relationship between drug concentration and platelet count reduction [Wang, 2010] including a feedback mechanism. According to the model predictions after repeat dosing at 100 mg every other week, no participant is anticipated to achieve a CTCAE grade 2 or greater reduction in platelet count.

The NOAEL in the 13 weeks cynomolgus monkey study was 300 mg/kg/week. The PK exposure achieved in cynomologous monkey was more than 100 times greater than the predicted PK exposure in human (steady state AUC 21300ug.h/mL and Cmax 68.2ug/mL) at a dose of 300 mg every other week [GlaxoSmithKline Document Number 2016N284919_00].

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. 18 years or over, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Documented diagnosis of systemic sclerosis as defined by the American College of Rheumatology / European League Against Rheumatism 2013 criteria (Van den Hoogen, 2013), with diffuse cutaneous involvement.
3. Modified Rodnan Skin Score (mRSS) ≥10 and ≤35 at screening.
4. In all cases, a disease duration of ≤60 months at screening, defined as time from onset of the first non-Raynaud's phenomenon manifestation.
5. Active disease defined by **at least one** of the following criteria at screening:
    - CRP ≥6 mg/l (0.6 mg/dL), that in the opinion of the investigator is due to SSc.
    - Disease duration ≤18 months at screening, defined as time from the first non-Raynaud's phenomenon manifestation.
    - Increase of ≥3 mRSS units, compared with an assessment performed within the previous 6 months.
    - Involvement of one new body area (according to mRSS definitions) and an increase of ≥2 mRSS units compared with an assessment performed within the previous 6 months.

- Involvement of two new body areas (according to mRSS definitions) within the previous 6 months.

6. An area of uninvolved or mildly thickened skin that in the opinion of the investigator would allow subcutaneous injection at one of the following locations:
   - Abdomen
   - Front, middle region of the thigh
   - Outer area of the upper arm
7. An area of involved skin (mRSS ≥1) on the forearm suitable for repeated skin biopsies to be collected as described in Section 9.8.2.
8. Participants who are taking mycophenolate mofetil (≤3,000 mg/day) or equivalent mycophenolate sodium (≤ 2160 mg/day) are permitted in the study if the participant has been on a stable dose for ≥3 months at the first dosing day (Day 1) and participant and investigator are willing to continue this dose until at least completion of the Day 85 (Week 12) visit. If mycophenolate was recently ceased, there must be ≥3 months between the date mycophenolate was ceased and the first dosing day (Day 1).
9. Participants who are taking oral corticosteroids (≤10 mg/day of prednisone or equivalent) are permitted in the study if the participant has been receiving a dose no greater than 10 mg/day for at least 4 weeks at the first dosing day (Day 1) and the investigator does not anticipate increasing the dose above 10 mg/day during the study.
10. Participants who are taking phosphodiesterase 5 (PDE5) inhibitors and endothelin receptor antagonists (including bosentan) are permitted in the study if the participant has been on a stable dose for at least 4 weeks for PDE5 inhibitors and for at least 3 months for endothelin antagonists at the first dosing day (Day 1) and participant and investigator are willing to continue this dose until at least completion of the Day 85 (Week 12) visit.
11. Participants who are taking non-immunosuppressive medications not specifically excluded in Section 6.2 are permitted in the study (e.g. hydroxychloroquine, angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor (AR) blockers, calcium-channel blockers and proton-pump inhibitors). However no new long-term medications and no dose-changes to existing long term medications are permitted during the two weeks prior to the first dosing day (Day 1). See Section 7.7.1.

Sex

12. Male and female participants

    a. Male participants:

    A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the dosing period and for at least 126 days (18 weeks) after the last dose of study treatment and refrain from donating sperm during this period.

b. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

(i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

OR

(ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 from 28 days prior to first dosing day (Day 1), during the dosing period and for at least 126 days (18 weeks) after the last dose of study treatment.

Informed Consent

13. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

1. Patients classified to the limited cutaneous SSc subset, as determined by the investigator.
2. Rheumatic autoimmune disease other than dcSSc including but not limited to rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, dermatomyositis, systemic vasculitis and primary Sjogren's syndrome, as determined by the investigator.
3. FVC ≤50% of predicted, or a diffusing capacity of the lung for carbon dioxide (DLCO) (corrected for haemoglobin) ≤40% of predicted at screening.
4. Pulmonary arterial hypertension, as determined by the investigator.
5. Clinically significant inflammatory myositis (related to SSc), as determined by the investigator.
6. SSc renal crisis within 6 months of the first day of dosing (Day 1).
7. History of clinically significant or uncontrolled cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major disease at screening not related to SSc and that in the opinion of the investigator would prevent participation in the study.
8. Known bleeding or coagulation disorder.
9. Major surgery (including joint surgery) within 3 months prior to screening, or planned during the duration of the study.
10. Clinically significant multiple or severe drug allergies (including to humanized monoclonal antibodies), intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema

multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

11. An active infection, or a history of infections as follows:
    - History of opportunistic infections that have not resolved by 6 months prior to the first day of dosing (Day1) or recurrent infection as determined by the investigator. This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or frequency.
    - A serious infection requiring treatment with IV antibiotics and/or hospitalisation, if the last dose of antibiotics or the hospital discharge date was within 3 months of the first day of dosing (Day1).
    - An acute or chronic infection requiring treatment with oral antibiotics or antiviral medications, if the last dose was received within 4 weeks of the first day of dosing (Day1).
    - Any active or unresolved bacterial, viral or fungal infection present on the first day of dosing (Day1), whether requiring treatment or not. This does not include fungal nail infections.
    - Active or past osteomyelitis, unless fully resolved in the opinion of the investigator.
    - Symptomatic herpes zoster that has not resolved by 3 months prior to the first day of dosing (Day1).
    - History of Tuberculosis (TB) or a positive QuantiFERON-TB Gold test or QuantiFERON-TB Gold PLUS test at screening.
        - If the QuantiFERON-TB Gold test or QuantiFERON-TB Gold PLUS test is indeterminate, it can be repeated once. A participant will not be eligible unless the second test is negative or they have a negative tuberculin skin test (defined as skin induration <5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin or other vaccination history).
        - There must be no other clinical evidence of TB on physical examination of the participant (screening examination).
12. Alanine transferase (ALT) >2x upper limit of normal (ULN) at screening.
13. Bilirubin >1.5xULN at screening (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
14. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

    NOTE: Participants with evidence of liver fat on imaging but who are otherwise eligible for the study criteria may be enrolled.
15. QTc >480 msec or QTc >500 msec in participants with Bundle Branch Block at screening.

16. A history of carcinoma in situ and malignant disease, with the exception of basal cell carcinoma that has been completely excised prior to the study.

Prior/Concomitant Therapy

17. Treatment with methotrexate within 3 months prior to the first dosing day (Day 1).
18. Previous or planned bone marrow transplant (e.g. autologous stem cell transplant).
19. Treatment with a biologic within the following timeframes:
    - Tocilizumab, abatacept or anti-TNF (including etanercept, infliximab, certolizumab, golimumab or adalimumab) within 3 months prior to the first dosing day (Day 1).
    - Rituximab within 12 months prior to the first dosing day (Day 1).
    - For any other biologic consult the medical monitor.
20. Treatment with oral or intravenous cyclophosphamide within 6 months prior to the first dosing day (Day 1).
21. Treatment with any other non-biologic systemic immunosuppressive medication (e.g. azathioprine, tacrolimus, ciclosporin) not mentioned above within 4 weeks prior to the first dosing day (Day 1), with the exception of mycophenolate and oral corticosteroid (which are permitted).
22. Treatment with topical immunosuppressive medications (e.g. topical corticosteroids, tacrolimus) within 1 week prior to the first dosing day (Day 1).
23. Treatment with intravenous prostanoids (e.g. iloprost) within 2 weeks prior to the first dosing day (Day 1) or planned treatment before the Day 85 (Week 12) visit.
24. Treatment with anti-fibrotic medications including tyrosine kinase inhibitors (e.g. nintedinib and imatinib) and pirfenidone within 3 months prior to the first dosing day (Day 1).
25. Live vaccine(s) within 4 weeks prior to the first dosing day (Day 1), or plans to receive such vaccines during the study.
26. Treatment with anti-coagulant medications, including warfarin, heparin, thrombin inhibitors, and Factor Xa inhibitors within 2 weeks prior to the first dosing day (Day 1).
27. Treatment with anti-platelet medications (e.g. clopidogrel, prasugrel, ticagrelor and dipyridamole) within 2 weeks prior to first dosing day (Day 1). This does not include aspirin at doses of 150 mg or less, or non-steroidal anti-inflammatory drugs, which are permitted.

Prior/Concurrent Clinical Study Experience

28. Current enrollment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study treatment.
29. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day (Day 1).

Diagnostic assessments

30. Any of the following at screening:
    - Haemoglobin <110 g/L
    - Platelet count <150x10^9/L
    - Estimated glomerular filtration rate (GFR) (MDRD calculation) of <45 mL/min/1.73m^2
31. A positive human immunodeficiency virus (HIV) antibody test at screening.
32. Presence of Hepatitis B surface antigen (HBsAg) at screening.
33. Positive Hepatitis B core antibody (HBcAb) test at screening.
34. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study treatment.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
35. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

    NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

Contraindications

36. Sensitivity to any of the study treatments or components thereof, or other allergy that in the opinion of the investigator, contraindicates participation in the study.
37. Where participation in the study would result in donation of blood or blood products in excess of a volume of 500mL during the study.
38. A history of drug and alcohol misuse that could interfere with participation in the trial according to the protocol, or in the opinion of the investigator impacts on the physical or mental wellbeing of the participant.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Participants will be required to fast for 12 hours (no food or drink, except water) prior to collection of the Day 1 and Day 85 (Week 12) clinical chemistry blood sample. There will be no other caffeine, xanthine or dietary restrictions for the rest of the study.

6.4. Screen Failures

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

Repeat assessments during the 42 day 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.

7. TREATMENTS

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

7.1. Treatments Administered

Syringes containing GSK2330811 or placebo will be prepared at the study site by an unblinded pharmacist or designee. Placebo will be sourced locally by the site while GSK2330811 will be provided by GSK. GSK2330811 or placebo will be administered by subcutaneous injection in to the abdomen, thigh or upper arm by the investigator or designee. Participants will remain at the clinic for observation for at least 30 minutes after each dose has been administered. See the Study Reference Manual (SRM) for further details.

Study Treatment Name:	**GSK2330811**	**Placebo**
Dosage formulation:	Solution for injection; 50 mM Sodium Acetate, 0.05 mM EDTA, 1.0% Arginine, 51 mM Sodium Chloride, pH 5.5 with 0.02% polysorbate 80	Normal Saline (0.9% w/v Sodium Chloride)
Unit dose strength(s)/Dosage level(s):	1.2mL fill with 1mL extractable volume at 100 mg/mL	Not applicable
Storage:	Store between 2-8°C, protect from light	As recommended by supplier

Study Treatment Name:	**GSK2330811**	**Placebo**
Route of Administration:	SC injection only	SC injection only
Dosing instructions:	Administered by investigator or designee. **Cohort 1 100 mg dose** 1 x 1ml injected via needle and syringe **Cohort 2 300 mg dose** 3 x 1ml injected via needle and syringe If a dose lower than 300 mg is required then the volume injected will be reduced accordingly.	Administered by investigator or designee. Injection volume and number of injections will match active doses administered.
Packaging and Labeling:	Study Treatment will be provided in vials and packed in 1 vial per carton. Each vial and carton will be labelled as required per country requirement.	
Manufacturer:	GSK	To be sourced locally

7.2. Dose Modification

- Initially, 4 participants will be randomised into cohort 1 and receive a dose of 100 mg GSK2330811 or placebo (Section 5.5). Cohort 1 may be expanded to 8 participants in the circumstances described below.
- Decisions regarding progression to cohort 2 will be made by the DRC, constituted as outlined in Appendix 3.
- After 4 evaluable participants (Section 5.2) have reached the end of the treatment period (Day 85,Week 12), the DRC will review all available safety and tolerability data for all randomised participants. Any available PK data will also be reviewed. Based on this review, the DRC will recommend one of:
    1. Progress to cohort 2 at a dose level of 300 mg GSK2330811 as planned.
    2. Progress to cohort 2 at a dose level ≥100 mg and <300 mg GSK2330811.
    3. Expand cohort 1 to recruit an additional 4 participants (3:1 ratio of GSK2330811 to placebo).
    4. Initiate a full safety review.

- If any of the following events occur during cohort 1, with a reasonable possibility of being related to GSK2330811, then cohort 1 will be immediately expanded to 8 participants at the same dose level:
    1. A participant receiving GSK2330811 experiences a Haemoglobin <80g/L (CTCAE Grade 3 or greater event) **or**
    2. A participant receiving GSK2330811 experiences a Platelet count <50x10^9/L (CTCAE Grade 3 or greater event) **or**
    3. A participant receiving GSK2330811 experiences an SAE, provided continued recruitment is approved by the DRC.

- **If cohort 1 is expanded**, the DRC will review all available safety and tolerability data for all randomised participants after 8 evaluable participants have reached the end of the treatment period (Day 85, Week 12). All available PK data will also be reviewed. Based on this review, the DRC will recommend one of:
    1. Progress to cohort 2 at a dose level of 300 mg GSK2330811.
    2. Progress to cohort 2 at a dose level ≥100 mg and <300 mg GSK2330811.
    3. Initiate a full safety review.

- If any of the following occur during cohort 1, with a reasonable possibility of being related to GSK2330811, then **treatment and recruitment will be halted** and a full safety review undertaken:
    1. 2 or more participants on GSK2330811 experience a Haemoglobin <80g/L (CTCAE Grade 3 or greater event) **or**
    2. 2 or more participants on GSK2330811 experience a Platelet count <50x10^9/L (CTCAE Grade 3 or greater event) **or**
    3. A participant on GSK2330811 experiences a Platelet count <50x10^9/L (CTCAE Grade 3 or greater event) **and** a different participant on GSK2330811 experiences a Haemoglobin <80g/L (CTCAE Grade 3 or greater event) **or**
    4. 2 or more participants on GSK2330811 experience an SAE.

A full safety review of cohort 1, if undertaken, will involve the analysis of unblinded data by the DRC and relevant GSK personnel (Appendix 3). If the study is halted and following the safety review a decision is made to recommence study treatment, progression to cohort 2 will only occur after notification of the appropriate Regulatory Authorities and Ethics Committees, according to local regulatory requirements.

CTCAE grades are defined using the CTCAE criteria V4.03: June 14, 2010 (refer to Appendix 8 for both SI and conventional units). If there is any concern that an abnormal laboratory result is spurious, a repeat test will be undertaken before implementing any of the actions described in this section.

7.3. Method of Treatment Assignment

At the time of signing the Informed Consent a unique participant number (eCRF Subject Number) will be assigned. The unique participant number will be used to identify individual participants during the course of the study.

All participants will be centrally randomized on Day 1 using an Interactive Web Response System (IWRS). Before the study is initiated, log in information & directions for the IWRS will be provided to each site. Participants will be assigned a unique number (randomisation number). Once a randomisation number has been assigned it must not be reassigned. The randomisation number encodes the participant's assignment to one of the 2 arms of the study, according to the randomisation schedule generated prior to the study by the Statistics Department at GSK.

Participants will be randomised to receive GSK2330811 or placebo in a 3:1 ratio.

7.4. Blinding

This will be a double blind (sponsor open) study where all study staff involved in the clinical assessments (which includes the investigator, sub-investigators and other site staff) and the participant will be blinded to treatment allocation.

An unblinded pharmacist or designee will be required at site to prepare and dispense the study treatment. The unblinded pharmacist will endeavour to ensure that there are no differences in temperature or in time taken to dispense following randomisation. The unblinded pharmacist is not permitted to communicate the participant's treatment allocation to blinded site staff.

Unblinded monitors will be assigned to review all pharmacy records, storage and procedures. In addition unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomisation/dispensing has been done accurately.

Sponsor open refers only to specific members of the DRC at defined meetings. Committee membership is defined in Appendix 3. Further details of blinding and how the integrity of the study will be maintained will be described in the DRC charter.

Unblinding of individual participants may occur to ensure appropriate management of a participant, e.g. if an SAE is considered by the investigator as being causally related to study treament, taking account of the points below:

- The investigator or treating physician may unblind a participant's treatment assignment only in the case of a medical emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.

- It is preferred (but not required) that the investigator first contacts the medical monitor or appropriate GSK study personnel to discuss options before unblinding the participant's treatment assignment.

- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding and within 24 hrs.

- The date and reason for the unblinding must be fully documented in the eCRF.

A participant may continue in the study if that participant's treatment assignment is unblinded, if it remains appropriate for them to do so.

GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

The IWRS will be programmed with blind-breaking instructions.

7.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for the preparation of GSK2330811 will be detailed in SRM.

1. The unblinded pharmacist or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment 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 treatment are provided in the Study Reference Manual.

- Under normal conditions of handling and administration, study treatment 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 /equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

Participants will be dosed at the site and will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment 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 treatment.

7.7. Concomitant Therapy

7.7.1. Permitted medications and Non-Drug Therapies

Medications for the treatment of SSc and concomitant diseases may be taken as long as they are not prohibited (Section 7.7.2) and as long as specific requirements listed in Table 1 are adhered to. All concomitant medications taken during the study will be recorded in the eCRF according to the guidelines listed in Table 1.

Any deviations from these specific requirements (for example increase in corticosteroid dose >10 mg/day) during screening, that cannot be addressed by extending the screening period up to a maximum of 42 days, will result in the participant being a screen failure. In this case they may be re-screened as described in Section 6.4.

Any deviations from these requirements during the study (for example, for an urgent clinical need) must be documented and may affect the evaluability of the participant. If safety concerns are raised by deviations from these requirements they must be discussed with the Medical Monitor, who will determine if discontinuation of study treatment is warranted.

Table 1 Specific requirements for permitted medications during the study

Medication	Requirement
Mycophenolate mofetil (up to 3,000 mg/day) OR equivalent mycophenolate sodium (up to 2160 mg/day)	Must have been on a stable dose for at least 3 months at the first dosing day (Day 1). Participants should remain on a stable dose at least until completion of the Day 85 (Week 12) visit (unless dose must be reduced because of a safety concern). If mycophenolate was recently ceased, there must be ≥3 months between the date mycophenolate was ceased and the first dosing day (Day 1). Record medication name and dose at first dosing day, and record dates and nature of any dose changes during study. All local standard of care practices and product labelling for mycophenolate including prophylactic therapies, contraception requirements, laboratory testing, follow up care and other precautions and contraindications

Medication	Requirement
	should continue to be followed throughout the study.
Oral corticosteroids (up to 10 mg/day prednisolone or equivalent, dose averaged over a 7 day period)	Must have been on a dose ≤10 mg/day for at least 4 weeks at the first dosing day (Day 1). Participants are encouraged to continue on a stable dose at least until completion of the Day 85 (Week 12) visit (unless dose must be reduced because of a safety concern). Doses above 10 mg/day are not permitted. Record medication name and dose at first dosing day, and record dates and nature of any dose changes during study. All local standard of care practices and product labelling requirements for oral corticosteroids including prophylactic therapies (including but not limited to calcium supplementation and gastric protection), laboratory testing, follow up care and other precautions and contraindications should continue to be followed throughout the study.
PDE5 inhibitors (including but not limited to sildenafil)	Must have been on a stable dose for at least 4 weeks at the first dosing day (Day 1). Participants should remain on a stable dose at least until completion of the Day 85 (Week 12) visit (unless dose must be reduced because of a safety concern). Record medication name and dose at first dosing day, and record dates and nature of any dose changes during study.
Endothelin receptor antagonists (including but not limited to bosentan)	Must have been on a stable dose for at least 3 months at the first dosing day (Day 1). Participants should remain on a stable dose at least until completion of the Day 85 (Week 12) visit (unless dose must be reduced because of a safety concern). Record medication name and dose at first dosing day, and record dates and nature of any dose changes during study.
Other permitted long-term (i.e. planned to continue for the duration of the study) concomitant medications not specifically mentioned above (for example, low dose aspirin, hydroxychloroquine, ACE-inhibitors, calcium-channel blockers, proton pump inhibitors)	May not be commenced and dose should not be altered during the 2 weeks prior to the first dosing day (Day 1). Participants are encouraged to continue these therapies on a stable dose at least until completion of the Day 85 (Week 12) visit (unless dose must be reduced because of a safety concern). Record medication name, indication if available and dose at first dosing day, and

Medication	Requirement
	record dates and nature of any dose changes during study.
Short-term therapies for symptoms (for example, paracetamol, non-steroidal anti-inflammatory drugs, antacids) or for intercurrent illnesses (for example, antimicrobials).	Permitted if not specifically prohibited (Section 7.7.2), but an AE report may be necessary depending on the indication for their use (Appendix 4) Record medication name, indication, dose and duration.
Topical therapies, vitamins and other dietary supplements (for example, iron supplements, folate).	Permitted except for topical immunosuppressive medications (Section 7.7.2). Therapies/supplements in this class of specific interest will be listed in the SRM and recorded in the eCRF.

7.7.2. Prohibited Medications and Non-Drug Therapies

Table 2 lists prohibited medications for defined periods of time before AND DURING the study until after the Day 197 (Week 28) visit. The two exceptions are iloprost and topical immunosuppressive therapies, which are only prohibited up to and including the Day 85 (Week 12) visit.

Participants who start prohibited medications or therapies (for example, for an urgent clinical need) during the treatment period (i.e. Day 1 to the Day 85 (Week 12) visit) will be required to permanently discontinue study treatment. Participants who start prohibited medications at any time during the study may also be withdrawn from the study at the discretion of the medical monitor. If in any doubt, investigators are advised to discuss medications with the medical monitor.

Table 2 Prohibited Medications

Medication	Time period prior to first dosing day
Topical immunosuppressive medications (e.g. topical corticosteroids, tacrolimus)	1 week (and until the Day 85 (Week 12) study visit inclusive)
Intravenous prostanoids (e.g. iloprost)	2 weeks (and until the Day 85 (Week 12) study visit inclusive)
Anticoagulant medications (including but not limited to warfarin, heparin, thrombin inhibitors and factor Xa inhibitors)	2 weeks
Antiplatelet medications other than aspirin ≤150 mg/day or non-steroidal anti-inflammatory drugs, including but not limited to clopidogrel, prasugrel, ticagrelor and dipyridamole	2 weeks
Live vaccines	4 weeks
Treatment with any form of non-biologic systemic immunosuppressive medication not mentioned elsewhere in this table (with the	4 weeks

Medication	Time period prior to first dosing day
exception of mycophenolate and oral corticosteroids up to 10 mg/d prednisolone or equivalent, which are permitted).	
Methotrexate	3 months
Tocilizumab, abatacept or any anti-TNF agent (including etanercept, infliximab, certolizumab, golimumab or adalimumab)	3 months
Antifibrotic medications including tyrosine kinase inhibitors (e.g. nintedinib and imatinib) and pirfenidone.	3 months
Cyclophosphamide (oral or intravenous)	6 months
Rituximab	12 months
Chlorambucil	Any prior exposure is not permitted
Any other licensed biologic agent not specifically mentioned above.	Consult medical monitor

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants will discontinue study treatment if an individual stopping rule is reached. In this event participants should continue the study (i.e. continue with study visits and assessments).

8.1.1. Individual Safety Stopping Rules

Study treatment will be permanently discontinued in the event of any of the following:

- If a participant experiences a serious or clinically significant severe AE that in the opinion of the investigator, after consultation with the medical monitor, has a reasonable possibility of relation to GSK2330811 (Appendix 4).
- The participant becomes pregnant.
- The participant initiates a prohibited medication (Section 7.7.2).
- The participant develops a serious infection.
- The participant experiences a severe or serious hypersensitivity reaction, including anaphylaxis (defined according to Sampson, 2006).
- The liver chemistry stopping criteria (Section 8.1.2), QTc stopping criteria (Section 8.1.3) or haematological stopping criteria (Section 8.1.4) are met.

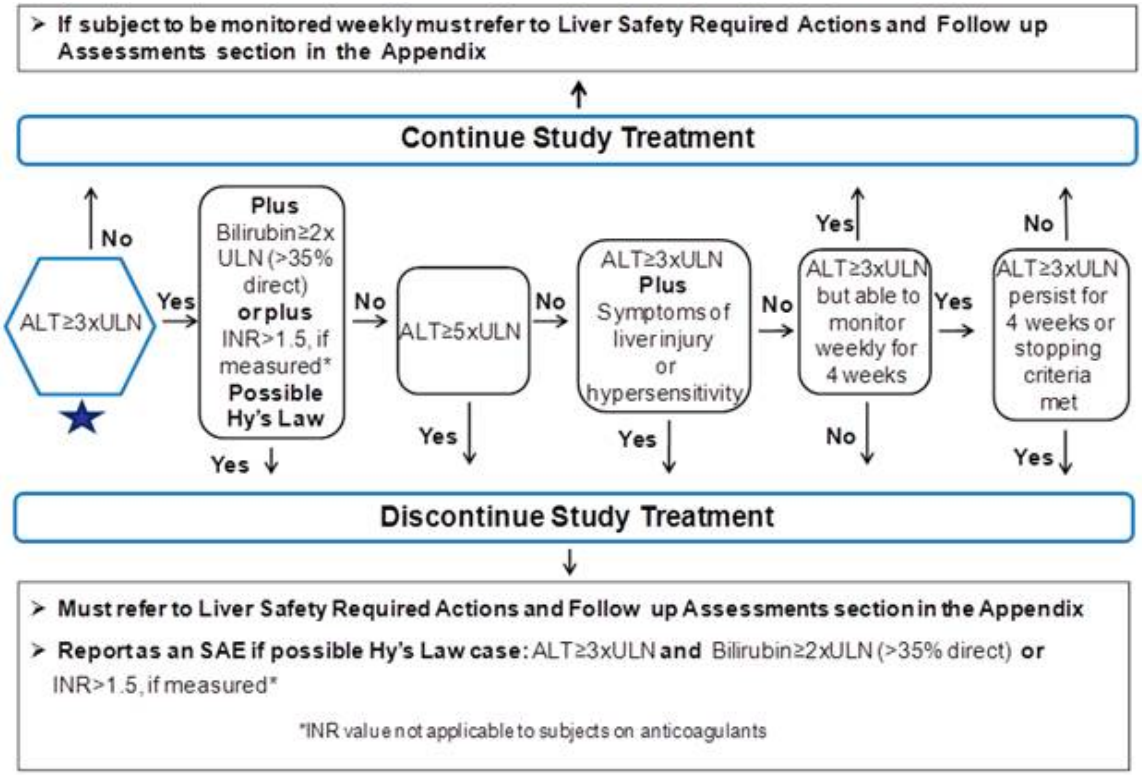
If the study treatment is discontinued, but the participant has received one or more doses of study treatment, the remaining study visits should still be performed including skin biopsy and home and laboratory FVC monitoring if this is deemed reasonable in the opinion of the Investigator and the participant is willing. In particular, the safety assessments should still continue as per protocol. The suction blister procedure will not be performed if study treatment is discontinued. If the participant declines any further follow-up and chooses to withdraw themselves from the study the investigator should make every effort to conduct the Early Withdrawal assessments as described in Section 8.2 and Section 2.

8.1.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.3. QTc Stopping Criteria

A participant who meets either of the bulleted criteria below, based on the average of triplicate ECG readings, will permanently discontinue dosing:

Discontinuation Criteria:

1. QTc >530 msec

2. Change from baseline: QTc >60msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g. 5-10 minute) recording period (see Section 9.4.3).

8.1.4. Haematological Stopping Criteria

Study treatment will be permanently discontinued for a participant if any of the following haematological stopping criteria are met:

- Haemoglobin <80g/L (i.e. CTCAE Grade 3 or greater event), confirmed by a repeat sample obtained before the next scheduled dose of GSK2330811.
    - If haemoglobin is <90g/L at any point during the dosing period (Day 1 to the Day 71 visit), a repeat haemoglobin will be required within 72 hrs of the next scheduled dose, with a result ≥80g/L obtained prior to dosing.
- Platelet count <$50x10^9$/L (i.e. CTCAE Grade 3 or greater event), confirmed by a repeat sample obtained before the next scheduled dose of GSK2330811).
    - If platelet count is <$100x10^9$/L during the dosing period (Day 1 to the Day 71 visit), a repeat platelet count will be required within 72 hrs of the next scheduled dose. Dosing may proceed if platelet count is ≥$75x10^9$/L (see also Section 8.1.5).

See Appendix 8 for CTCAE criteria in both SI and conventional units.

8.1.5. Temporary Discontinuation

Study treatment for a participant will be temporarily withheld if the most recent platelet count taken within 72 hours of the scheduled dose is ≥$50x10^9$/L and <$75x10^9$/L . In this event, scheduled study visit assessments should be performed but the dose must **NOT** be administered.

Once platelet count is $\geq 75 \times 10^9/L$ study treatment may resume with the next scheduled dose.

8.1.6. Interrupted Dosing

8.1.6.1. Study Treatment Restart or Rechallenge

If study treatment is stopped for any reason other than a temporary discontinuation as outlined in Section 8.1.5 it will not be restarted.

8.1.6.2. Missed Doses

A missed dose is defined as a participant not receiving a dose during the visit window. If a study treatment dose is missed and a temporary or permanent discontinuation of treatment criterion has not been reached (see Section 8.1) then this will be reported as a protocol deviation. Study treatment will continue at the next scheduled dosing visit. 'Catch-up' doses must not be administered between study visits.

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The Early Withdrawal Visit will only be performed if the participant withdraws from the study and therefore will not undertake any further scheduled visits. The early withdrawal visit will only be performed if the participant is willing (see Section 2 for assessments to be performed at this visit).

8.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she 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/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Section 2 (Schedule of Activities).
- If an on-site visit is not possible due to the COVID-19 pandemic, a virtual or telephone visit can be performed for any study assessments that can be conducted remotely (e.g. AE/SAE review & concomitant medication review) at the Day 113, Day 155, Day 197 and Early Withdrawal (if required) visits. The AE/SAE review and concomitant medication review should be conducted in a manner as similar as possible (in terms of language and approach) as would have taken place with an in-person clinic visit.
- 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 treatment.
- 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.
- 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.
- All samples (blood, urine, blister fluid or skin biopsy) will be retained for a maximum of 15 years after the last participant completes the trial.

Order of Assessments throughout the study

Scleroderma Health Assessment Questionnaire (SHAQ), Physician Global Assessment of Disease Activity, 12-lead ECG and vital signs should occur before the blood draw. On the study visits where the assessments include a skin biopsy or suction blister these should be performed after the mRSS assessment and blood draw.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM. The SRM will provide the site personnel with administrative and detailed technical information that does not impact participant safety.

Screening Assessments

Information collected during the screening assessments described below represents key data that identifies and defines the participant's status.

Informed Consent: Informed consent will be obtained from the participant prior to initiation of any study procedures or study-specific data collection.

During the screening period screening assessments will be performed as outlined in the Section 2 and include:

Demographic parameters: Will be captured: year of birth, sex, race and ethnicity.

Medical history: Will be assessed as related to the inclusion/exclusion criteria listed in Section 6 (as detailed in the eCRF).

Respiratory Tests:

1. Respiratory Laboratory Tests (FVC and DLCO) for Eligibility.
Hospital based lung function equipment will be used to measure lung function tests and be overseen by a respiratory physiologist. Lung function tests will be recorded whilst the participant is in a sitting position (if taken whilst the participant is on the bed, their legs should be over the edge) and may be repeated, until technically acceptable measurements have been made. The respiratory laboratory measured FVC and DLCO will be recorded in the eCRF.

2. Home Spirometry (FVC).
The rate of decline in daily FVC, measured at home via a hand held spirometer, in patients with IPF has been shown to be highly predictive of outcome and subsequent mortality (Russell, 2016). Training on use of the hand held spirometer will be given during the screening visit and a refresher course offered at Day 1. After initial training, three FVC readings will be obtained and recorded by the participant at the first screening visit. The participant will then continue to measure weekly FVC on a day convenient to them throughout the screening period and until the end of the study. The participant will enter the readings into their paper diary. The paper diary entries will be transcribed into the eCRF.

Baseline Assessments taken at Day 1 only

Autoantibodies: To aid patient characterisation and potential future stratification a blood sample will be taken on Day 1 for assessment of autoantibody status, including but not limited to Anti-Scl-70, Anti-centromere and Anti-RNAPIII.

Medical History: Medical history will include SSc-related factors, smoking and cardiovascular medical history / risk factors and information from the participant's most recent lung HRCT scan, if available, as detailed in the eCRF.

9.1. Efficacy Assessments

9.1.1. FVC

Respiratory Laboratory Test

FVC will be measured using hospital based lung function equipment at the timepoints specified in Section 2 and will be overseen by a respiratory physiologist, as described for screening tests in Section 9.

Home Spirometry

Weekly FVC (triplicate readings), at a day convenient to the participant, will be performed by the participant using a hand held spirometer and entered into the participant's paper diary, as described for screening tests in Section 9.

9.1.2. Scleroderma Health Assessment Questionnaire (SHAQ)

The participant will complete a Scleroderma Health Assessment Questionnaire (SHAQ) (Steen, 1997; Pope, 2011) at the time points specified in Section 2. The SHAQ is comprised of:

- The Health Assessment Questionnaire Disability Index (HAQ-DI) (21 items across 8 domains) that assesses physical function
- 6 individual Visual Analogue Scales assessing the impact of each of the following symptoms on activities of daily living:
    - Pain
    - Gastrointestinal involvement
    - Lung involvement
    - Vascular (Raynaud's Phenomenon)
    - Digital Ulcers
    - Patient Global Assessment of Disease Activity

The SHAQ will be completed by the participant during scheduled clinic visits and before any other assessments.

9.1.3. Physician Global Assessment of Disease Activity (PhGA)

The investigator or physician designee only will complete a global assessment of disease activity using the physician global assessment (PhGA), at the time points specified in Section 2. This is a single item numeric rating scale (See SRM for full details).

Note:

The same investigator or physician designee should perform all PhGA assessments for a participant for the duration of the study.

9.1.4. Patient Global Assessment of Disease Activity (PtGA)

The participant will complete a global assessment of disease activity using the patient global assessment (PtGA), at the time points specified in Section 2. This is a single item numeric rating scale (See SRM for full details).

The PtGA will be completed by the participant during scheduled clinic visits and before any other assessments.

9.1.5. Modified Rodnan Skin Score (mRSS)

The mRSS provides an evaluation of skin thickness rated by clinical palpation using a 0–3 scale [redacted]) for each of 17 surface anatomic areas of the body (Clements, 1995; Czirak, 2008). These individual values are added and the sum is defined as the total skin score and will range from 0 to 51. The mRSS will be performed at the time points specified in Section 2.

Note:

The same investigator or physician designee should perform all mRSS assessments for each participant for the duration of the study.

9.1.6. Composite Response Index in diffuse cutaneous Systemic Sclerosis (CRISS)

Data for the Composite Response Index in dcSSc (CRISS) will be collected at the timepoints described in Section 2. The CRISS implements a two-step algorithm to calculate a probability that a participant's disease status has improved from its baseline value (Khanna, 2016).

Step 1: Participants who develop new or worsening cardio, pulmonary and/or renal involvement due to SSc are considered to have not improved (irrespective of improvement in other core items) and are assigned a CRISS score (probability) of 0.

Step 2: For the remaining participants, the CRISS score (probability) is calculated from change from baseline in the five core items:

- mRSS

- % predicted FVC
- HAQ-DI
- PhGA
- PtGA

See SRM for further details in conducting this assessment.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any 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 treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

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

All SAEs will be collected from the signing of the ICF until Day 197 (Week 28, final follow-up visit) at the time points specified in Section 2.

All AEs will be collected from the start of treatment (Day 1) until Day 197 (Week 28, final follow-up visit) at the time points specified in Section 2.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of the site becoming aware, as indicated in Appendix 4. 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 in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.

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 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment 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 according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until Day 197 (Week 28, final follow-up) visit.

- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of GSK2330811 greater than 100 mg SC every other week for cohort 1 and 300 mg (or other dose as determined by DRC) SC every other week for cohort 2 after taking into account visit windows, 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 within 48hrs of the site becoming aware.
2. Monitor the participant at least weekly for AE/SAE and laboratory abnormalities (including but not limited to full blood count / complete blood count and liver function tests) for 2 weeks, and thereafter as advised by the Medical Monitor.
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose in the CRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in Section 2.

9.4.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height 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).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

Single vital signs will be measured in a seated or semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3. Electrocardiograms

12-lead ECGs will be obtained as outlined in Section 2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.3 for QTc withdrawal criteria.

Where single ECG measurements are obtained, if the QTc measurement fulfils a QTc withdrawal criterion an additional two QTc readings will be obtained and the average of these three measurements will be used.

When triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to Section 2 for the timing and frequency. The tests include routine clinical safety laboratory assessments and additional haematology assessments related to mechanisms of anaemia and thrombocytopenia.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. 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 during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SRM and the Section 2.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), this must be documented in the eCRF.

9.4.5. Immunogenicity Assessments

Serum samples from whole blood will be collected as specified in Section 2. Washout samples will be collected at the follow-up visit to minimise interference of circulating study treatment in the antibody assessments. Testing will be performed using a tiered approach involving screening, confirmation and titration [EMA, 2010; FDA, 2009]

performed by Clinical Immunology, GlaxoSmithKline. If sera contain potential anti-GSK2330811 antibodies in the screening assessment, they will be confirmed by immunocompetition 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).

9.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of GSK2330811 at the time points specified in Section 2. The actual date and time (24-hour clock time) of each sample will be recorded. Plasma analysis will be performed by PTS-Bioanalysis, GlaxoSmithKline. Concentrations of GSK2330811 will be measured in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. Instructions for the collection, processing, storage and shipping procedures are provided in the SRM.

9.6. Pharmacodynamics

9.6.1. OSM Target Engagement in Blood

Blood samples will be collected for measurement of serum levels of free and total OSM protein at the time points specified in Section 2. Analysis will be performed by Clinical Immunology, GlaxoSmithKline using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. Instructions for the collection, processing, storage and shipment of the samples will be described in the SRM.

9.7. Genetics

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

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

The following samples for biomarker research are required and will be collected from all participants in this study at the timepoints specified in Section 2:

- Blood
- Plasma
- Serum

- Skin Biopsy

In addition, an optional skin suction blister procedure will be performed at selected sites for consenting participants enrolled in cohort 2. Suction blister fluid will be collected between the Day 57 (Week 8) visit and the Day 85 (Week 12) visit inclusive.

The results of some of the exploratory biomarker investigations (for example proteomic and transcriptomic analysis in blood samples) may be reported separately from the main clinical study report.

9.8.1. Exploratory Biomarkers in Blood

Serum and plasma samples for blood biomarkers including CRP will be collected at the timepoints specified in Section 2, to explore changes in levels in response to GSK2330811. Note a CRP measurement is taken at more clinical visits than the remaining exploratory biomarkers. Instructions for the collection and handling of biological samples will be described in the SRM. Markers may include (but are not restricted to):

- Fibrosis markers, such as enhanced liver fibrosis (ELF) test and markers of collagen turnover.
- Inflammation markers, such as IL-6 and CRP.
- Vasculopathy markers, such as vWF and VEGF.

Completion of biomarker analysis or emerging evidence in the scientific literature may trigger further transcriptomic and proteomic analysis for determining the impact of GSK2330811 on pathways of interest and for research related to SSc. Transcriptomic analysis may be conducted on blood samples using microarray technology, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for a skin biopsy sample. The same samples may also be used to confirm findings by application of alternative technologies.

In addition serum samples may undergo proteomic analysis using SomaLogic SOMAscan and / or alternative equivalent technologies which facilitate the simultaneous measurement of multiple protein species resulting in a proteomic profile. Instructions for the collection and handling of biological samples will be described in the SRM.

9.8.2. Exploratory Biomarkers in Skin Biopsy

Two skin punch biopsies, 3 mm in size, will be collected from clinically involved skin (mRSS $\geq$ 1), preferably hairless, on the forearm of participants, on Day 1 (pre-dose) and also on Day 85. All biopsies for a participant should be collected from the same forearm following SRM recommendations. At both timepoints, one biopsy sample will be evaluated histologically while the second biopsy sample will be evaluated by transcriptomic analysis. Biopsy quality assessments may be performed during the study

as described in the SRM. Details of the biomarker skin biopsy sample processing, storage, quality assessments and shipping procedures are provided in the SRM.

Histopathological assessments of the biopsy will explore changes in levels of disease biomarkers (protein and / or mRNA and / or pathological evaluation) in response to GSK2330811. Markers may include (but are not restricted to):

- Fibrosis markers, such as αSMA to assess changes in myofibroblast numbers.
- Inflammation markers, such as changes in numbers of CD3+ T cells.
- Vasculopathy markers, such as changes in CD31+ endothelial cells.

Transcriptomic analysis will determine the effect of GSK2330811 on OSM and disease related gene expression. Gene expression will be measured using microarray technology, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for a skin biopsy sample. The same samples may also be used to confirm findings by application of alternative technologies. Genes may include but are not restricted to:

- OSM related genes such as SOCS3 and JAK2.
- Fibrosis markers, such as THBS1 and COMP.

9.8.3. PK and PD in Suction Blister Fluid

Skin suction blisters provide a minimally invasive opportunity to study skin PK and PD [Kuhns, 1992]. The dermal suction blister fluid is representative of skin interstitial fluid without affecting normal dermal vascular endothelium [Worm, 1981].

Participants at selected sites have the option to undergo a dermal suction blister assessment between the Day 57 (Week 8) visit and Day 85 (Week 12) visit inclusive. Suction blister fluid is required from a minimum of 6 participants on GSK2330811 in order to explore the PK and target engagement of GSK2330811 in skin. Participants who do not wish to participate in the blister assessment may still participate in the study. Suction blisters will be induced over a period of approximately 2 hours on involved skin (mRSS $\geq$ 1), preferably hairless, of either forearm. Blister fluid will then be aspirated.

Details of the induction, aspiration, processing, storage and shipping of samples will be described in the SRM.

Markers may include (but are not restricted to):

- Total OSM
- PK
- Free OSM

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

No formal sample size calculations have been conducted as the sample size is based on feasibility.

The primary objective is safety and tolerability, where for cohort 1 an initial cohort of four participants will be randomised to either GSK2330811 or placebo in a 3:1 ratio. In cohort 2 a minimum of approximately 20 and a maximum of 36 participants will be randomised to GSK2330811 or placebo in a 3:1 ratio.

Table 3 illustrates the credible interval for observed safety events in the GSK2330811 group in cohorts 1 and 2. This uses a Bayesian approach assuming a non-informative conjugate prior distribution Beta(1,1). This illustrates that if one event in three participants is observed, for example, then a true rate of 0.806 for that safety event cannot be ruled out.

Table 3 Inferences on the true event rate

Study Cohort	Observed event rate (events / treated participants)	Upper limit of 95% credible interval for the true event rate
Cohort 1 (N=3)	0/3	0.602
	1/3	0.806
	2/3	0.932
	3/3	0.994
Cohort 2 (N=15)	0/15	0.206
	1/15	0.302
	2/15	0.383
	3/15	0.456

For information, for the exploratory endpoint of fibrosis log (PIIINP) assuming an SD=0.521 (Lee, 2001) and a sample size of 15 participants receiving GSK2330811 and 5 receiving placebo, it is estimated that the lower and upper bounds of the 95% confidence interval for the comparison of GSK2330811 to Placebo will be within 0.565 of the point estimate. This calculation is based on a two tailed Type I error rate of 5%. The difference in log (PIIINP) between healthy volunteers and Systemic Sclerosis patients was 0.42 in an observational study (Lee, 2001).

Within the defined range, the final number of participants recruited may depend on an interim sample size re-estimation.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Safety	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
Pharmacokinetic	The 'PK Population' is defined as participants in the 'Safety' population who received an active dose and for whom a pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only. In the case of PKPD, the Safety Population is used so that participants receiving placebo can be included.

All participants that receive at least 4 doses of GSK2330811 or placebo and have biopsies at both Day 1 and the Day 85 (Week 12) assessment will be considered evaluable.

10.3. Statistical Analyses

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary and Secondary	No formal statistical testing will be performed on safety data. If deemed appropriate posterior probabilities of the true rate of an adverse event of interest may be calculated using a non-informative prior distribution. Clinical interpretation will be based upon review and displays of adverse events, disease related events, laboratory values and vital signs. The principal consideration in this evaluation will be the investigator-reported relationships of either adverse events or laboratory abnormalities to investigational product. Safety data including immunogenicity data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standard. Target Engagement will be presented in tabular and graphical format and summarized descriptively according to GSK's IDSL standard for Pharmacodynamic endpoints. Sparse blood sampling is being implemented in this study to allow the full pharmacokinetic profile for each participant to be reconstructed using Bayesian prediction from a population pharmacokinetic model using Non Linear Mixed Effect Model (NONMEM) version VII or higher and determine the exposure over the dosing interval (AUC (0- τ)), apparent systemic clearance (CL/F), and apparent volume of distribution (Vss/F). Plasma GSK2330811 concentration data will be presented in tabular and graphical format and summarized descriptively according to GSK's IDSL standards.
Exploratory	Will be described in the reporting and analysis plan (RAP).

10.3.2. Other Analyses

PK, pharmacodynamic and biomarker exploratory analyses will be described in the RAP.

The analysis approach for exploratory biomarkers will be:

- Relationships between endpoints, explored graphically and using statistical measures of consistency if data allow.
- Profiles / Trends over time of individual endpoints

- Inference using posterior probabilities of the true within participant change from baseline and true between group treatment difference using non-informative prior distributions.

In addition to the univariate analysis of the change from baseline in each biomarker, a multivariate analysis of endpoints of several biomarkers of fibrosis may also be performed.

The primary between-group analysis will be between the placebo and GSK2330811 groups. However if a difference in baseline levels of key biomarkers of fibrosis is observed by mycophenolate use then an alternative primary comparison will be considered.

The following PK/PD analyses will be conducted if data permit:

- To examine the relationship between plasma concentrations of GSK2330811, and target OSM concentration (total).

- To examine the relationship between plasma concentrations of GSK2330811, and platelet count.

10.3.3. Interim Analyses

In line with routine pharmacovigilance, an internal GSK SRT will review blinded safety data at appropriate intervals during the study conduct. See Appendix 3 for further details.

For the purposes of dose escalation a dose escalation review will occur once the appropriate data from cohort 1 has been collected. This dose escalation review along with the interim analyses outlined below will be conducted by the DRC. The activities of these and how the study integrity will be maintained are included in the DRC charter.

For the purpose of assessing target engagement, an unblinded interim analysis of PD and PK data will occur once an appropriate number of cohort 2 participants have completed the day 57 (Week 8) visit. The baseline total OSM and mean target engagement relative to the modelled predictions will be considered.

An interim analysis may be conducted to assess the baseline variability of key biomarkers once at least 16 participants have been randomised into cohort 2 of the study. This may lead to the adjustment of the biomarker assessment strategy.

An unblinded sample size re-estimation may be conducted once approximately 16 participants from cohort 2 complete the day 85 (Week 12) visit, where the key systemic biomarkers will be reviewed. This may lead to an increase in the sample size up to a maximum of 40 participants.

In addition to the formal planned interim analyses, further data reviews may be carried out by the DRC and/or senior managers not involved in the study conduct to aid in internal decision making. These reviews will have no impact on the conduct of the study.

The RAP will describe the planned interim analyses in greater detail.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACE	Angiotensin Converting Enzyme
ADA	Anti-drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AR	Angiotensin II Receptor
AST	Aspartate Aminotransferase
AUC	Area Under Concentration-Time Curve
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRISS	Composite Response Index in diffuse cutaneous Systemic Sclerosis
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
dcSSc	Diffuse Cutaneous Systemic Sclerosis
DLCO	Diffusion Capacity of the Lungs for Carbon Monoxide
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
HAQ-DI	Health Assessment Questionnaire Disability Index HAQ-DI
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HDL	High density lipoproteins
HIV	Human Immunodeficiency Virus
hr	Hour(s)
HRT	Hormone Replacement Therapy
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IL-6	Interleukin 6
IP	Investigational Product
INR	International Normalised Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
L	Litre
LDL	Low Density Lipoproteins
LIF	Leukemia Inhibitory Factor
LLN	Lower Limit of Normal
mAb	Monoclonal Antibody
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCP-1	Monocyte Chemotactic Protein 1
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
mRNA	Messenger Ribonucleic Acid
mRSS	Modified Rodnan Skin Score
msec	Milliseconds
NOAEL	No Observed Adverse Effect Level
OSM	Oncostatin M
OSMR	Oncostatin M Receptor
PD	Pharmacodynamic
PDE5	Phosphodiesterase 5
PhGA	Physician Global Assessment
PK	Pharmacokinetic
POM	Proof of Mechanism
PtGA	Patient Global Assessment
QTc	QT Duration Corrected for Heart Rate
QTcB	QT Duration Corrected for Heart Rate by Bazett's Formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
SAE	Serious Adverse Event(s)
SC	Subcutaneous
SD	Standard Deviation
SHAQ	Scleroderma Health Assessment Questionnaire
SOP	Standard Operating Procedure
SRM	Study Reference Manual

SRT	Safety Review Team
SSc	Systemic Sclerosis
t	Time of last observed quantifiable concentration
TB	Tuberculosis
TE	Target Engagement
TMDD	Target-Mediated Drug Disposition
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
Vss/F	Steady State Volume of Distribution / Bioavailability
vWF	Von Willebrand Factor
WBC	White Blood Cells
WOCBP	Women of Child Bearing Potential

Trademark Information

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NONMEM
QuantiFERON-TB Gold
QuantiFERON-TB Gold PLUS
SOMAscan

12.2. Appendix 2: Clinical Laboratory Tests

The tests and calculations detailed in Table 4 and Table 5 will be performed by the central laboratory or (for calculated values) by GSK. Local laboratory results are required in the event that a participant has a haemoglobin of <90g/L or a platelet count of $<100x10^9$/L during the dosing period (Day 1 to Day 71). A local laboratory result may also be acceptable with pre-approval by GSK.

In circumstances where it is not possible to obtain bloods at site or ship bloods to the central lab due to the COVID-19 pandemic, scheduled safety (standard hematology and clinical chemistry) labs and pregnancy tests for the Day 113, Day 155, Day 197 and Early Withdrawal (if required) visits should be performed if feasible and may be performed locally at the clinical site or within the community (all at the discretion of the Investigator).

If a local sample is required for haemoglobin or platelet count, the results must be entered into the eCRF. A simultaneous unscheduled sample should also be sent for central analysis.

The tests detailed in Table 4 and Table 5 represent a minimum set of assessments and this list may be expanded if determined necessary by the sponsor.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Standard Hematology	RBC Count Haemoglobin Haematocrit MCV MCH MCHC RDW	Platelet Count Mean Platelet Volume Reticulocyte Percentage Absolute Reticulocyte Count Reticulocyte Production Index[1]	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[2]	Potassium Sodium Corrected Calcium **At screening only[3]** TSH FT4	Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Alkaline Phosphatase (ALP) Lactate Dehydrogenase (LD) **Lipids (fasted)[4]** Total Cholesterol HDL	Urea Creatinine eGFR[5] Glucose[6] Total bilirubin Direct bilirubin Albumin Total Protein

Laboratory Assessments	Parameters		
	FT3 INR APTT	LDL Triglycerides	
Routine Urinalysis	• Specific gravity, pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)		
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) [7] • Serology (HIV antibody, HBsAg, HBcAb and hepatitis C virus antibody) • QuantiFERON-TB Gold / QuantiFERON-TB Gold PLUS		

NOTES :

1. Calculated value based on reticulocyte percentage/count and haematocrit.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.2 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).
3. Blood for TSH, FT4, FT3, INR and APTT will be taken at screening only.
4. Blood for lipid tests (fasted) will be taken at predose on Day 1 and Day 85 (Week 12) only.
5. Calculated value. Estimated GFR will be calculated using the MDRD formula.
6. Glucose on Day 1 and Day 85 will be fasted glucose, all other timepoints will be random glucose.
7. Serum pregnancy testing will be performed at screening, Day 197 (Week 28) and early withdrawal visit and urine pregnancy testing will be performed at all other visits unless serum testing is required by local regulation or IRB/IEC. Pregnancy testing on dosing days must be performed prior to administration of study treatment. If it is not possible for a serum pregnancy test to be performed due to the COVID-19 pandemic, a urine pregnancy test should be performed if possible.

Table 5 Additional HaematologyAssessments

Time Point	Parameters
Screening, Day 1, Day 85 (Week 12) and Day 197 (Week 28) AND if any haematology stopping rule (at the next visit) OR early withdrawal is fullfilled	Serum Ferritin % Transferrin saturation Serum B12 Serum folate
Day 1, Day 85 (Week 12) and Day 197 (Week 28)	Serum Haptoglobin TPO EPO

Time Point	Parameters
AND if any haematology stopping rule (at the next visit) OR early withdrawal is fullfilled	
Day 1 and Day 85 (Week 12)	Blood Film

To maintain blinding only results of safety laboratory assessments will be reported to the investigative sites or other blinded personnel. No other laboratory data (e.g. PK, target engagement and biomarkers) will be provided until study completion.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, 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

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- 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.

The ICF will contain a section that addresses the use of remaining samples for exploratory research. Participants will be told that they may withdraw their consent at any time and for any reason during the storage period.

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/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/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.

Committees Structure

12.3.1. Safety Review Team (SRT)

Oversight of study safety will be provided by a sponsor Safety Review Team (SRT). The SRT will conduct in-stream review of blinded safety data including AE, SAEs, vital signs and laboratory data at appropriate intervals during the study (at a minimum after 4, 8 and 12 participants have reached Day 85 (Week 12)). The membership of the SRT will include the GSK Medical Monitor, GSK Statistician and a GSK Global Clinical Safety and Pharmacovigilance representative or appropriate designees.

The SRT may decide to alter the study conduct at any time to ensure participant safety and any such changes to study conduct for safety reasons will be promptly communicated to the appropriate Regulatory Authorities and IRB/IEC. Additional detail regarding the composition and actions of the SRT will be included in the SRT charter.

12.3.2. Data Review Committee (DRC)

The DRC will conduct the dose escalation and interim analysis reviews of the data. No members of the study team involved in the direct day to day conduct of the study or in the acquisition of data will take part in the DRC. Full details of membership, timing, blinding and decision-making framework for DRC reviews will be described in the DRC charter. The DRC membership will vary according to the meeting as follows:

Dose escalation: All available safety, tolerability and PK data from cohort 1 will be reviewed by the GSK Study Physician(s), GSK Pharmacokineticist and GSK Statistician or appropriate designees.

Interim Analyses: For the assessment of the baseline variability of key systemic biomarkers and GSK2330811 target engagement, membership will mirror those involved in the dose escalation decisions. The unblinded assessment of the disease biomarkers may also be reviewed, as part of the DRC, by the GSK Biology Lead, GSK Early Development Leader and GSK Senior Stakeholders.

The DRC may also conduct unblinded reviews on an ad hoc basis if required in accordance with the DRC charter.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter 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.

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 randomisation codes for their site only after completion of the full statistical analysis.

- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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 (eg, 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.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- 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 after study completion 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. GSK has defined the retention period as 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary.

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 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.

Study and Site Closure

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

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

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

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

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 treatment 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 treatment 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT 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 (eg, 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.

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 (eg, 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:
a. Results in death
b. 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.
c. 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.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 sufficiently 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 treatment 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 treatment 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 t GSK within 24 hours of receipt of the information.

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 for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- 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 contacts for SAE reporting 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 contacts for SAE reporting. • 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.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the dosing period and for at least 126 days (18 weeks) after the last dose of study treatment:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 6 when having penile-vaginal intercourse with a woman of childbearing potential.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- Refrain from donating sperm for the duration of study.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to ONE of the following from 28 days prior to first dosing day (Day 1), during the dosing period and for at least 126 days (18 weeks) after the last dose of study treatment:

- A barrier method (male condom or female diaphragm) and one highly effective method of contraception used consistently and correctly as described in Table 6.
- Two complementary highly effective methods of contraception used consistently and correctly as described in Table 6.
- Abstinence from heterosexual intercourse as described in Table 6 if this is their preferred and usual lifestyle on a long-term and persistent basis.

Table 6 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*

Sexual abstinence
(*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP will only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.
- Additional pregnancy testing must be performed on the day of and prior to each dosing during the treatment period and at each visit during the follow-up period and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Urine pregnancy testing will be performed using the test kit provided by the central laboratory in accordance with instructions provided in its package insert.
- Serum Pregnancy testing will be performed and assayed in the central laboratory.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.

- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will discontinue study treatment.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2330811 and / or SSc and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2330811 (or study treatments of this drug class), and SSc. Genetic research may consist of the analysis of one or more candidate genes or analysis of the entire genome
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2330811 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2330811 (or study treatments of this class) or SSc continues but no longer than 15 years after the last participant completes the study or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • 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 chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • 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 following the occurrence of an event.[5] • 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

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• 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 (CRF) page **<u>For bilirubin or INR criteria:</u>** • 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). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment 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, 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)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; HbsAg and HBcAb (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study

treatment prior to PK blood sample draw on the CRF. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.8. Appendix 8: Haematological Grades for Stopping Criteria (CTCAE criteria, V4.03: June 14, 2010)

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Platelet count decreased	<LLN – 75,000/mm^3 ; <LLN -75.0 x 10^9/L	<75,000 – 50,000/mm^3; <75.0- 50.0 x 10^9/L	<50,000 – 25,000mm^3; <50.0- 25.0 x 10^9/L	<25,000mm^3; <25.0 x 10^9/L	
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Anemia	Haemoglobin (Hgb) <LLN -10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 -4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of haemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					

12.9. Appendix 9: Country-specific requirements

No country-specific requirements exist at this time.

12.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).
Amendment 4 12-Nov-2018

Overall Rationale for the Amendment: This amendment was executed to provide clarification on the points detailed below:

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities 6.2 Exclusion Criteria 12.2 Appendix 2: Clinical Laboratory Tests	Updated to reflect use of QuantiFERON-TB Gold PLUS test at central laboratory.	Clarification to support update to central laboratory process
6.1 Inclusion Criteria 7.7.1 Permitted medications and Non-Drug Therapies	Wording clarified to reflect intent that mycophenolate sodium dose allowed should be equivalent to mycophenolate mofetil dose.	Clarification
10.1 Sample Size Determination 10.3.3 Interim Analyses	Updated text from 'will' to 'may' to indicate that it may not be feasible to conduct all interim analyses.	Updated to add flexibility
12.2 Appendix 2: Clinical Laboratory Tests	Wording updated to clarify circumstances when local laboratory results are acceptable	Clarification

Amendment 3 (20-Jul-2017)

Overall Rationale for the Amendment: This amendment was primarily executed to add the additional exploratory endpoints of change in the Composite Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) and change in Patient Global Assessment.

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities	Updated to include Patient Global Assessment of Disease Activity (PtGA) and CRISS data collection at Day 1, Day 85 and Day 197.	Required for calculation of the Composite Response Index in diffuse cutaneous Systemic Sclerosis (CRISS).
4 Objectives and Endpoints	Updated to include the exploratory endpoints of 'Composite Response Index in diffuse cutaneous Systemic Sclerosis (CRISS)' and 'Change from baseline in Patient Global Assessment of Disease Activity (PtGA)'.	To enable calculation of the CRISS as an exploratory endpoint.
5.2 Number of Participants, Treatment Arms and Duration	Statement added to clarify that participants in Cohort 1 are not eligible to participate in Cohort 2.	Clarification
6.1 Inclusion Criteria 7.7.1 Permitted Medications and Non-Drug Therapies	Statement added to inclusion criterion 8 and Table 1 to clarify that 'If mycophenolate was recently ceased, there must be ≥3 months between the date mycophenolate was ceased and the first dosing day (Day 1)'.	Clarification
6.1 Inclusion Criteria	Inclusion criterion 11 updated to remove the word "other" for clarity.	Clarification
6.2 Exclusion Criteria	Note added to exclusion criterion 14 to clarify that 'Participants with evidence of liver fat on imaging but who are otherwise eligible for the study criteria may be enrolled'.	Clarification

Section # and Name	Description of Change	Brief Rationale
9.1 Efficacy Assessments	Updated to include 9.1.4 Patient Global Assessment of Disease Activity (PtGA) and 9.1.6 Composite Response Index in diffuse cutaneous Systemic Sclerosis (CRISS).	To enable calculation of the CRISS as an exploratory endpoint.
9.8.3 PK and PD in Suction Blister Fluid	Refined the duration of the blister procedure.	To provide a more accurate description of the method.
10.3.1 Safety Analyses	Updated to remove 'and derived pharmacokinetic parameters'.	The individual parameters derived from population pharmacokinetic models will not be summarised. The population-level parameter will be used directly where appropriate.
10.3.3 Interim Analyses	Updated text on 'reviews' of data to clarify that these may also be conducted by senior managers not involved in the conduct of the study. Statement added to clarify that reviews will have no impact on the conduct of the study.	Clarification
Appendix 1: Abbreviations and Trademarks	Minor typographical changes.	Clarification

Amendment 2 (12-Dec-2016)

Overall Rationale for the Amendment: This amendment was primarily executed in response to an FDA recommendation for a 30 minute observation period after each dose is administered.

Section # and Name	Description of Change	Brief Rationale
7.1 Treatments Administered	Updated to include 30 minute observation period after each dose.	Response to FDA recommendation
8.1.1 Individual Safety Stopping Rules	Reference to criteria for defining anaphylaxis has been included (Sampson 2006).	Response to FDA recommendation
7.7.1 Permitted Medications and Non-Drug Therapies 7.7.2 Prohibited Medications and Non Drug Therapies	Wording clarified to make it clear that treatment may be modified for an urgent clinical need.	Response to FDA recommendation
10.3.3 Interim Analyses	Clarified that DRC may also review available data for internal decision making.	Clarification
7.1 Treatment administered 7.4 Blinding	'Or designee' added for the unblinded pharmacist role, to align with wording in Section 7.5.	Clarification
9 Study Assessments and Procedures 12.2 Appendix 2: Clinical Laboratory Tests	Minor clarification changes.	Clarification
3.3.1 Risk Assessment	Minor typographical changes and spaces between words.	Presentation

Amendment 1 (01-Nov-2016)

Overall Rationale for the Amendment: This amendment was executed in response to the FDA request that the participant eligibility criteria be modified to include two forms of contraception for males and females of childbearing potential.

Section # and Name	Description of Change	Brief Rationale
6.1. Inclusion Criteria	To include 2 forms of contraception for male and female participants	Response to FDA request
Appendix 5 Contraception Guidance	To include 2 forms of contraception for male and female participants	Response to FDA request

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 5	01-Apr-2020
Amendment 4	12-Nov-2018
Amendment 3	20-Jul-2017
Amendment 2	12-Dec-2016
Amendment 1	01-Nov-2016
Original Protocol	13-Sep-2016

Type of Protocol Amendment	Numbering	Type of changes
Global	Amendment 4	New changes for all
Global	Amendment 3	New changes for all
Global	Amendment 2	New changes for all
Global	Amendment 1	New changes for all