Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP) for Dose Escalation and Target Engagement Interims

Title	:	Reporting and Analysis Plan for Dose Escalation and Target Engagement Interims for study 201247: 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.
Compound Number	:	GSK2330811
Effective Date	:	Refer to Document Date

Description:

The scope of this version of the RAP is to document the outputs required for the dose escalation, first interim analysis (target engagement),second interim (baseline variability) and final reporting efforts.

This RAP describes the planned analyses and output to be included in the Clinical Study Report for Protocol 201247.

This RAP will be provided to the study team members to convey the content of the deliverables.

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TABLE OF CONTENTS

PAGE

1. INTRODUCTION

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

Protocol Revision Chronology:		
2016N269831_00	13-Sep-2016	Original
2016N269831_01	01-Nov-2016	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.
2016N269831_02	12-Dec-2016	This amendment was primarily executed in response to an FDA recommendation for a 30-minute observation period after each dose is administered. It included a clarification that the DRC may also review available data for internal decision making.
2016N269831_03	20-Jul-2017	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. It further clarified that the 'internal decision making' referred to version 2 would not affect the conduct of the study and may involve or be carried out by senior stakeholders. In addition, it specified that derived PK parameters will not be summarised. PK data will be analysed using a Population PK model. Although this will provide individual participant parameters, the appropriate way of summarising these is by referring to the Population PK model itself, not by summarising the individual participants' parameters.
2016N269831_04	12-Nov-2018	To clarify that the mycophenolate sodium dose allowed is equivalent to the mycophenolate mofetil dose, add clarification around use of local labs and flexibility to the timing of the interim analyses.
2016N269831_05	01-Apr-2020	In response to the COVID-19 pandemic, schedule of activities (Section 2 in the protocol) updated to extend visit windows, allow virtual/ telephone visits and allow safety labs and pregnancy tests to be run locally during the off-treatment follow-up period.

1.1. RAP Amendments

Revision chronology and planned versions:

Version	Status	Date final	Scope
Final	Final	20-Feb-2018	Update from critical components RAP. Updated to cover Dose escalation, Extended dose escalation, Interim Analysis 1
Amendment 1	Final	14-Dec-2018	Additional detail around Interim Analysis 1 and Interim Analysis 2
Amendment 2	Final	04-Jun-2019	Additional details added around biomarkers to be explored in Interim Analysis 2. Initial details around the outputs for Interim Analysis 3 (if occurs) and the Final Analysis.
Amendment 3	*Planned*	*NA*	Removed reference to Interim analysis 3 in alignment with updated data review committee (DRC) charter. Added all details required for Final Analysis.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1. Changes from the DRC charter are outlined in Table 2.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
All available safety, tolerability and PK data from cohort 1 will be reviewed	In addition, PD data from cohort 1 will be reviewed	The study team has decided that an early review of target engagement at the low dose during the dose escalation interim would be beneficial for the project.
Defined enrolled population as all subjects who signed the ICF	Separated out the enrolled population into screened (signed ICF) and enrolled (randomized).	To allow clearer separation between screen failures and participants who passed screening but did not receive study treatment.

Table 2 Changes to Analysis Plan defined in DRC charter

DRC	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
In interim analysis 1, the overview of data to be reviewed includes: "Safety including Immunogenicity"	Immunogenicity data will not be provided as unavailable at the time of reporting and so will not form part of reporting effort IA1	Immunogenicity data is unlikely to be conclusive at this early interim. If there are unexpected PK observations, then the study team may request that the immunogenicity samples are run.
At interim 2, the question was posed 'Does concomitant medication alter biomarkers sufficiently to warrant changing recruitment strategy?' based on the guideline ' Exploratory graphical analysis of the effect of concomitant medication and selected demographic factors on baseline levels of key decision-making biomarkers will be reviewed alongside the fitting of a statistical model.'	The impact of concomitant medication on baseline biomarkers will not be explored at interim 2 and no statistical models using concomitant medications will be fitted.	There is no intention to update the protocol and change the recruitment strategy at this time.
At interim 2, data planned to be reviewed was baseline biomarker, safety and population	In addition to the planned data, PK and PD outputs will be produced.	Allow updating of PK/PD modelling.

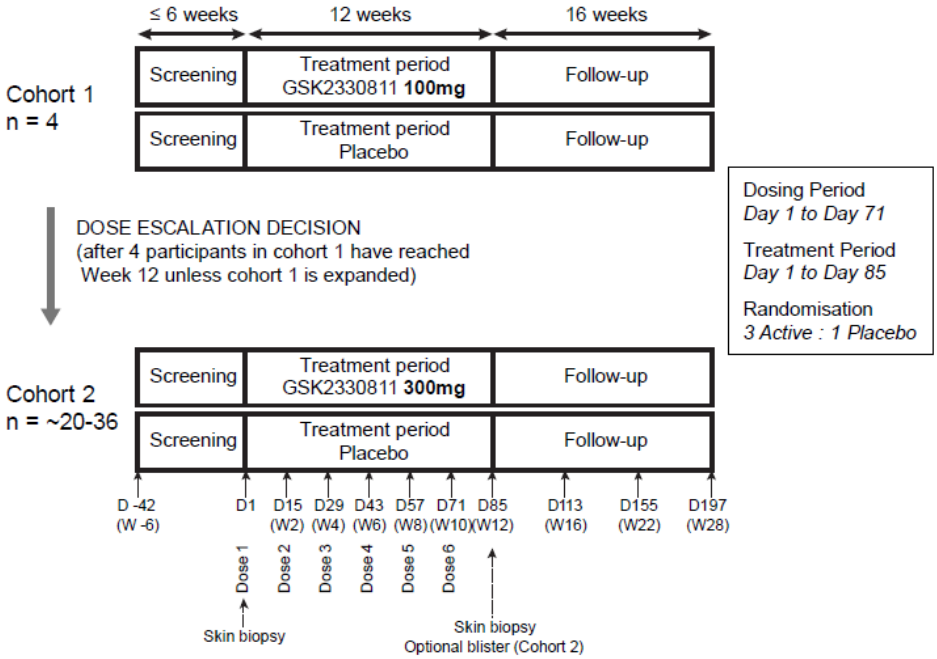
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
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 Objectives	**Secondary Endpoints**
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
Exploratory Objectives	**Exploratory Endpoints**
To explore the pharmacology of repeat	• Endpoints may include (but are not limited to):

Objectives	Endpoints
subcutaneous doses of GSK2330811 and its effects on biomarkers of fibrosis, inflammation and vasculopathy in the blood and skin of participants with dcSSc	▪ 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)
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.

2.3. Study Design

Overview of Study Design and Key Features



Design Features	○ 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 has 2 sequential cohorts. A minimum of approximately 24 participants and a maximum of 40 participants will be randomized across two cohorts. Participants will be randomised in a 3:1 ratio within each cohort to GSK2330811 and placebo respectively. In cohort 1, a minimum of 4 participants and in cohort 2, a minimum of approximately 20 participants will be randomized to either GSK2330811 or placebo. • Cohort 1 will be used to evaluate a repeat-dose, predicted to provide sub-maximal inhibition of Oncostatin M (OSM). Once at least 4 evaluable participants of Cohort 1 have reached the end of the treatment period, a dose escalation decision will be made. If the dose is not escalated one pre-defined option is an extension of recruitment at the current dose level (extended dose escalation). If the dose is escalated, cohort 2 will then be used to evaluate a repeat-dose, predicted to provide maximal inhibition of OSM. In cohort 2 treatment allocation will be stratified according to mycophenolate concomitant medication status treated or nontreated. • 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 participants will then 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.

Overview of Study Design and Key Features	
	• Participants will enter a follow-up period of approximately 16 weeks, after the treatment period. • The duration of the study, including screening, will be up to 34 weeks for participants.
Treatment Assignment	• Participants will be randomised in a 3:1 ratio within each cohort to GSK2330811 and placebo respectively, in cohort 2 this randomisation will be stratified by Mycophenolate use.
Dosing	• At least 4 participants in Cohort 1 will be randomised to receive a dose of 100 mg GSK2330811 or placebo, recruitment into this dose level may be expanded at the recommendation of the Data Review Committee (DRC). • After these participants have reached the end of the treatment period on Day 85, the Data Review Committee (DRC) will review and recommend the dose level for the active arm of Cohort 2 as either 300 mg or >=100 mg and <300 mg.
Interim Analysis	See Table 5.

2.4. Statistical Analyses

2.4.1. Primary endpoints

For the primary endpoints (safety and tolerability) no statistical analysis is planned and therefore no formal statistical hypothesis will be tested.

2.4.2. Secondary endpoints

For the secondary endpoints (PK, PD and Immunogenicity) no statistical analysis is planned and therefore no formal statistical hypothesis will be tested. If data allow a simultaneous PopPK and PKPD model will be constructed by CPMS to describe PK and the relationship between PK and PD.

2.4.3. Exploratory biomarker endpoints

Exploratory biomarker analysis will take place for final SAC. An estimation approach using Bayesian methods will be undertaken.

Biomarker endpoints are described in Section 13.

2.4.4. Exploratory efficacy endpoints

Exploratory efficacy analysis will take place for final SAC. An estimation approach using Bayesian methods will be undertaken.

Clinical endpoints are described in Section 14.

3. PLANNED ANALYSES

3.1. In-stream and Interim Analyses

3.1.1. Safety Review Team (SRT)

In line with routine pharmacovigilance, an internal GSK SRT will review blinded safety data at appropriate intervals during the study conduct.

The following description of data provision and Statistics and Programming (S&P) tasks is provided for context:

3.1.1.1. Extract from SRT charter:

- After the week 12 data for 4, 8 and 12 participants have been received, Data Management will:
    - Coordinate the loading of data into Spotfire
    - Provide Statistics and Programming with raw data for LAB parameters (i.e. the LAB DM dataset). This will have in-stream QC applied but will not be formally cleaned to ensure timeliness.
- Statistics and Programming will provide blinded, grouped graphical representation of the restricted/blinded laboratory endpoints as specified in [Appendix 12]
- In addition, Q2 Solutions will provide results in Result View on an on-going basis

3.1.1.2. SRT reporting details

- The restricted lab parameters, not available in Spotfire or Result View to those with blinded access (an interactive system provided by the contract research organisation/ central laboratory for viewing results) are shown in Table 5.

Table 3 Restricted (blinded) parameters

Parameter	Category
Platelet Count	Safety
Haemoglobin	Safety
Haematocrit	Safety
RBC count	Safety
CRP	Biomarker

- S&P will produce summary tables and Figures for the restricted safety parameters (i.e. not CRP), these will be presented blinded (i.e. without revealing treatment allocation). Appendix 12 contains details of outputs that will be produced for the 'SRT' reporting effort (see 'Deliverable' column).

- In addition to the planned reviews in the SRT charter, the study team plan SRTs after 4, 8 and 12 participants have reached day 85 and an SRT may be called at any time. It is the study team's intention to time SRT's as efficiently as possible so that the safety review will inform DRC meetings.

- For the purposes of planning, Table 4, below, shows a likely scenario for SRT reporting efforts:

Table 4 Likely Timing of Initial SRT Reporting Efforts

Reporting effort	Timing
SRT 1	After 4 participants reach week 12 in cohort 1 (prior to DEC)
SRT 2	After 4 participants reach week 12 in cohort 2 (assuming escalation after 4 participants)
SRT 3	After 8 participants reach week 12 in cohort 2 (may be timed to coincide with IA1)
SRT 4	After 12 participants reach week 12 in cohort 2

- Note: To ensure study safety, additional SRTs will be conducted during the course of the study in line with the scope and frequency of the SRT charter.

- Unless otherwise specified outputs for the SRT will be based on the safety population.

3.2. Data Review Committee (DRC)

Data will be reviewed by a DRC at appropriate intervals throughout the study in order to make decisions on study conduct and ensure participant safety, in collaboration with the SRT (see Table 4 for details). A DRC charter describes the responsibilities and conduct of the DRC and how the integrity of the study, including blinding, will be maintained. This RAP describes the details of the analyses and outputs that will be provided for the DRC meetings. Table 5 provides an overview of the DRC meetings and the data that will be reviewed in them. The paragraphs below describe the interim analyses. A version of the RAP covering the outputs for each reporting effort will be agreed prior to interim analyses.

Table 5 Summary of Interim Analyses

Reason for analysis (reporting effort / deliverable title)	Interim analysis trigger	Data domains included in analysis (not all data from the domain will be reported).	S&P to receive unblinded (restricted) data
Dose Escalation (DE)	4 evaluable participants of Cohort 1 reach week 12	• Safety • PK • Total OSM (serum) • Free OSM (serum) • Population including concomitant medication	Y
Expanded Dose Escalation (Expanded DE, will only occur if required)	8 evaluable participants of Cohort 1 reach week 12 (Conditional)	• Safety • PK • Total OSM (serum) • Free OSM (serum) • Population	Y
IA1 Target Engagement (IA1)	Approximately 8 participants from Cohort 2 complete week 8 visit	• Total OSM in serum, and blister fluid, if available[1] • Free OSM in serum • PK in plasma and blister fluid, if available[1] • Safety • Population	Y
IA2 Baseline Variability (IA2)	Approximately 16 participants from Cohort 2 provide baseline sample	• Total OSM in serum, and blister fluid, if available[1] • Free OSM in serum • PK in plasma and blister fluid, if available[1] • Baseline systemic fibrosis and other biomarkers • Safety • Population	Y
Additional DRC Review Meeting		• Total OSM • Free OSM • PK in plasma • Safety • Population	Y
1: Note that it is the intention that PK and PD from Blister Fluid will be analysed in batches at the same frequency as plasma/serum.			

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 (IA2) 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.

The DRC may also review available data at additional points during the study for internal decision making.

An additional DRC was conducted following the request of safety review at the project level response to a temporary stopping criterion related to thrombocytopaenia being met in another study with GSK2330811 (Study 208564; A phase 1, randomised, double-blind, placebo-controlled study of the safety, tolerability, pharmacokinetics and pharmacodynamics of single subcutaneous doses of GSK2330811 in healthy Japanese participants).

The population for each output is specified in Appendix 12; unless otherwise specified the outputs for the DEC will be based on the safety population whereas the non-safety outputs for the later interims will be based on the per-protocol population to provide an assessment of repeat dose GSK2330811.

3.3. Final Analyses

3.3.1. DBF timeline

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

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprises of participants who sign the Informed Consent • Note Re-screened participants will be considered only once with their last Subject Id.	• Screen Failures
Enrolled	• Comprises of participants who ultimately pass screening, even if rescreened. • Note that this population includes both randomised participants and participants where no treatment was assigned (e.g. never randomised) even though they passed screening. Screen failures are excluded from the enrolled population unless they are successfully rescreened and enrolled.	• Study Population (selected outputs, Appendix 12)
Safety	• Comprises of all randomised participants who receive at least one part of one dose of study treatment. • This population will be based on the treatment the participant actually received.	• Study Population • Safety including Immunogenicity • PD for IA1 and IA2 • Systemic biomarkers for IA2
Pharmacokinetic (PK)	• Comprises of participants in the 'Safety' population who received an active dose and for whom a PK sample was obtained and analysed.	• PK • PK/PD (including PopPK model)
Per Protocol (PP)	• Comprises of participants in the 'Safety' population who comply with the protocol. • Protocol deviation that would exclude participants from PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 • PP population will only be derived for SAC. • This population will be based on the treatment the participant actually received.	• Study Population (selected outputs, Appendix 12) • PD (not incl. IA1 or IA2) • Systemic biomarkers • Skin Histology • Skin Gene Expression • Clinical efficacy
Suction Blister (SB)	• Comprises of participants in the 'Safety' population who signed the informed consent for Suction Blister, a blister sample was obtained and analysed.	• PK • PK/PD

Population	Definition / Criteria	Analyses Evaluated

NOTES:

- Please refer to Appendix 12 which details the population to be used for each display being generated.
- The safety population will be used for PD analysis in IA1 and IA2, as there will be limited subject data for the PP population due to partial data.

4.1. Protocol Deviations

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

Important deviations which result in exclusion from the per protocol analysis population will also be listed if they occur. (Please refer to Appendix 1

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan **[Version 7, 17 Dec 2019].**

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

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

A separate table and listing of all COVID-19 related protocol deviations will be provided to capture the impact on visits and assessments.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description [3]	Description [2]	Order [1]
A	GSK2230811 100 mg **SC - PARALLEL**	GSK2330811 100 mg	2
B	GSK2230811 300 mg **SC - PARALLEL**	GSK2330811 300 mg	3
P	Placebo **- PARALLEL**	Placebo	1

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.
2. If there is no space for the full drug name, and the full drug name is in the title or elsewhere on the output then the dose amount (i.e. 100mg or 300mg) may be used with consultation with statistician
3. This RAP instruction corrects a mistake in the Treatment Description field in the RANDALL NG.

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

1. GSK2330811 100 mg vs Placebo
2. GSK2330811 300 mg vs Placebo

Or, in short form when full drug name is shown in title or elsewhere on table, listing or Figure and after consultation with statistician:

1. 100 mg vs Placebo
2. 300 mg vs Placebo

5.2. Cohort Display Descriptors

After the DEC reporting effort has completed, use the RANDALL dataset to create a derived variable “cohort” for use with SRT outputs which are blinded. All participants in schedules 1 and 2 will belong to cohort 1, all other participants are in cohort 2.

Cohort Group Descriptions		
RandAll NG	Data Displays for Reporting	
Randall NG Schedule	Cohort	Order [1]
Schedule 1	1	1
Schedule 2	1	1
Schedule 3	2	2

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

5.3. Baseline Definitions

The column 'Baseline Label Used in Data Display' shows the preferred baseline for a parameter but if this is missing or a later, unscheduled, assessment exists then the latest pre-dose assessment will be used for that participant unless otherwise specified. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline unless otherwise specified.

Parameter	Study Assessments Considered as Baseline		Baseline Label Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Primary endpoints			
Safety			
12-Lead ECG		X	Day 1 (Pre-Dose) [Note: Triplicate]
Vital Signs		X	Day 1 (Pre-Dose)
Lab		X	Day 1 (Pre-Dose)
Urinalysis		X	Day 1 (Pre-Dose)
Secondary endpoints			
PD			
Serum OSM free and total		X	Day 1 (Pre-Dose)
Blister OSM total			No baseline
PK			
Plasma PK		X	Day 1 (Pre-Dose)
Blister PK			No baseline
Immunogenicity			
Immunogenicity		X	Day 1 (Pre-Dose)
Exploratory endpoints			
Efficacy			
mRSS		X	Day 1 (Pre-Dose)
Respiratory Laboratory FVC		X	Day 1 (Pre-Dose)
Home Spirometry FVC		X[1]	Day 1
SHAQ /PhGA /PtGA /CRISS[2]		X	Day 1 (Pre-Dose)
Disease biomarkers			
CRP		X	Day 1 (Pre-Dose)
Blood biomarkers		X	Day 1 (Pre-Dose)
Biopsy mRNA		X	Day 1 (Pre-Dose)
Biopsy IHC		X	Day 1 (Pre-Dose)

Parameter	Study Assessments Considered as Baseline		Baseline Label Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Mechanistic haematology		X	Day 1 (Pre-Dose)

NOTES:

1: The day 1 Home Spirometry FVC (which will be taken on site) is not mandated by the protocol to be pre-dose. If the home spirometry is taken post Day 1 dose, then the latest screening observation prior to dosing will be used as baseline.

2: CRISS is a measure of change and events over a time period, starting at Day 1.

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

5.3.1. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit – Baseline) / Baseline]
Ratio to baseline	= Post-Dose Visit / Baseline
Nadir	= Lowest post-baseline value of endpoint for a participant [1]
Days to Nadir	= Study Day of Nadir – 1[1]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum absolute change
Minimum value at timepoint	= The lowest value of the parameter in the reported group at the specified timepoint.

NOTES:

- 1: When there are multiple instances of the lowest value then the nadir used for reporting will be the earliest occurrence of that value.
- Unless otherwise specified, the baseline definitions specified in Section 5.3 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all absolute summary and change from baseline plots. 'Note: Baseline is defined as the pre-dose Day 1 assessment, unless unavailable, in which case it is the latest pre-dose assessment.'
- If there are multiple measurements (i.e. ECG) the derivation will be based on the average values where available.

5.4. Multicentre Studies

In this multicentre global study, it is expected that the number of participants from any one site will be low and there are no plans to stratify, summarise or analyse results by centres or country.

5.5. Examination of Covariates, Other Strata and Subgroups

5.5.1. Covariates and Other Strata

- The following is a list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses (see the statistical analysis sections for each class of data for details).
- Additional covariates of clinical interest may also be considered.

Category	Covariates
Mycophenolate status: • Mycophenolate use • No mycophenolate use	Mycophenolate status on Day 1 will be used as an explanatory variable in some analyses of exploratory endpoints (to be specified in the relevant statistical analysis sections). This category will not be used unless specified for an output.

5.5.2. Examination of Subgroups

There are no planned subgroup analyses due to the small overall study size.

5.6. Multiple Comparisons and Multiplicity

There is no adjustment for multiplicity in this phase 2a study where the primary endpoint of interest is safety and tolerability of the study treatment.

5.7. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
16.3	Appendix 3: Assessment Windows
16.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
16.5	Appendix 5: Data Display Standards & Handling Conventions
16.6	Appendix 6: Derived and Transformed Data
16.7	Appendix 7: Reporting Standards for Missing Data
16.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "Safety" population, unless otherwise specified. Screen failures will be listed based on the "Screened" population.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Concomitant systemic sclerosis and other medications will be summarised separately but listed together.

Bespoke outputs for this population include Systemic Sclerosis Disease and Medication History, Mycophenolate use at Day 1 and Autoantibody profiles (Historical collected from eCRF and Baseline).

Historical autoantibodies and positive baseline autoantibodies will be summarized. All non-negative data along with collected results for anti-RNAPIII antibody will be listed except for Anti-nuclear antibodies which will list both positive (including patterns and titres) and negative results. The below table explains the autoantibody labels used for displays.

Sorting Order	Historical Autoantibody	Baseline Autoantibody	Table/Listing labels	Plot [1]
1	ANA (anti-nuclear antibodies)	Anti-nuclear antibody	Anti-nuclear antibodies	O
2	Anti-RNAPIII	RNA Polymerase III Antibody - Standard	Anti-RNAPIII	R
3	Anti-Scl-70	Scl-70 Antibody	Anti-Scl-70	T
4	Anti-centromere	Anti-centromere Antibody	Anti-centromere	C
5		Anti-Smith antibody	Anti-Smith antibody	O
6		Anti-U1 RNP	Anti-U1 RNP	O
7		Jo-1 Antibody	Jo-1 Antibody	O
8		Sjogrens SS-A Antibody	Sjogrens SS-A Antibody	O
9		Sjogrens SS-B Antibody	Sjogrens SS-B Antibody	O
Note: [1] Added to subject with positive autoantibodies in the legends of Biomarker and Efficacy individual plots.				

Details of the planned displays are presented in Appendix 12.

7. SAFETY ANALYSES

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

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12.

Summaries of Platelet Count, Haemoglobin, Absolute Neutrophil Count and Red Blood Cell (RBC) count Nadir will also be produced to describe the anticipated effect of GSK2330811 on these cells. The nadir is defined as the lowest post-baseline value observed for each parameter. Correlation analysis will be performed and presented as scatter plots including Pearson correlation coefficient for Platelet and Haemoglobin nadir by treatment groups.
Table 6 lists the Haematology parameter groups that will be referenced in Appendix 12. These are required because some outputs will only be produced for selected haematological/laboratory parameters to monitor potential platelet and RBC effects that were observed in the first time in human study (group 1) and to meet the exploratory objective 'To characterise the mechanisms of any observed haematological effects of GSK2330811' (group 2).

Table 6 Haematology/Chemistry parameter groups

Haematology/ Chemistry parameter group name	Parameters	Reported under
Additional Chemistry Parameter[1]	Haptoglobin, Ferritin, Vitamin B12 and Folate.	Safety – Chemistry
Group 1 – Potential Haematology Signal	Haemoglobin, Red Blood Cells, Platelet Count, Reticulocytes, Absolute Neutrophil Counts	Safety – Haematology
Group 2 – Mechanistic Haematology/ Chemistry	Reticulocyte Production Index (See Section 16.6.4 for derivation), Immature Reticulocyte Fraction	Biomarkers
	Thrombopoietin (TPO) (Collected under Coagulation parameter), Erythropoietin (EPO), % Transferrin saturation	Biomarkers
Note: [1] Summarizes all collected chemistry parameters but Figures are based on only subset of parameters.		

For the purpose of calculating 'worst case' laboratory result summaries, Post-Baseline is defined as an occurrence after first dose of the treatment until the final follow up visit, see Section 5.3 and Appendix 3 for baseline definition.

7.3. Other Safety Analyses

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

All ECG summaries and listings will report both QTcF and QTcB which will be derived where necessary. If data is captured using another QTc method this will only be reported in listings.

A separate listing to capture the COVID-19 infection assessment of participants based on new eCRF page will be provided.

The details of the planned displays are presented in Appendix 12.

8. IMMUNOGENICITY ANALYSES

The Immunogenicity analyses will be based on the “Safety” population, unless otherwise specified. The immunogenicity analysis summarises the incidence of anti-drug antibodies and lists the titre of immunogenicity results.

Details of the planned displays are presented in Appendix 12.

9. PHARMACOKINETIC ANALYSES

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Correlation analysis will be performed and presented as scatter plots including Pearson correlation coefficient for Measured Steady State Concentration vs Baseline Body Weight, Haemoglobin and Platelet Nadirs as Percentage Change from Baseline vs Measured Highest Concentration by treatment groups.

9.1. Primary Pharmacokinetic Analyses

See Section 10 for PopPK analysis and Section 12 for PK/PD analysis.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

GSK2330811 plasma and Total OSM serum concentration-time data will be analysed by population pharmacokinetic/pharmacodynamic (PopPK/PD) methods using a non-linear mixed-effects modelling approach.

The objective of the PopPK analysis is to develop a population PK model that characterizes the PK of GSK2330811 following repeat subcutaneous administration in patients with dcSSc. The individual participant PK parameters will be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses.

10.1. Statistical Analyses / Methods

See Appendix 10 for details.
To support this analysis a PK/PD dataset will be generated. The details for the dataset specifications are provided in Appendix 9

10.1.1. Endpoint / Variables

10.1.1.1. Drug Concentration Measures

Refer to Appendix 5(Section 16.5.3 Reporting Standards for Pharmacokinetic)

10.1.1.2. Derived Pharmacokinetic Parameters

In addition to the parameters of the PopPK model itself, individual participant parameters will be estimated from the PopPK model i.e. empirical Bayes estimates will be reported (also known as post-hoc parameter estimates).

Parameter	Parameter Description
Apparent Clearance	Individual participant estimate of apparent clearance (empirical Bayes estimates)
Apparent Volume of Distribution	Individual participant estimate of apparent volume of distribution (empirical Bayes estimates)
AUC	Individual model predicted AUC at steady state

- **NOTES:** Additional parameters may be included as required.

10.1.2. Summary Measure

The population PK parameter will be used to describe the population so therefore parameters will not be summarised across participants.

10.1.3. Population of Interest

The standalone PopPK analysis will be based on the “Pharmacokinetic” (PK) population, unless otherwise specified. If the simultaneous PopPK/PD model can be developed, then the analysis will be based on the PK population.

10.1.4. Strategy for Intercurrent (Post-Randomization) Events

PK and PK/PD models will use all available data and will not account for intercurrent events (i.e. will adopt a 'while on treatment' strategy).

10.1.5. Statistical Analyses / Methods

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

11. PHARMACODYNAMIC ANALYSES

The endpoints OSM Free and OSM Total make up the primary pharmacodynamic endpoints in this study. Data will be presented in graphical and/or tabular form and will be summarized descriptively. Individual results will be reported in listings and Figures; summary results will be reported in tables and Figures.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

OSM Free and OSM Total will be analysed through the PK/PD models specified in Appendix 10.

The objective of this analysis is to develop a population PK/PD model that characterizes the PK of GSK2330811 and the total OSM concentration-time profile following repeated subcutaneous administration of GSK2330811 in patients with dcSSc.

Exposure/ response analysis for haematology (platelets and haemoglobin) will be a pooled analysis that includes all available clinical data generated with GSK2330811. This pooled analysis will be described in a separate document.

Exposure/ response and or joint analysis for clinical endpoints and biomarkers will be done ad-hoc post SAC, based on the results of the statistical analysis.

12.1. Statistical Analyses / Methods

The analysis aims to characterise the relationship between plasma concentrations of GSK2330811, and target OSM concentration (total). Predicted TE% will be derived as defined in Section 16.6.5. Predicted values for free OSM will be used if measured values are below the LLQ of the assay.

Detailed PK/PD methodology is presented in Appendix 10

To support this analysis a PK/PD dataset will be generated. The details for the dataset specifications are provided in Appendix 9

Any exposure/ response and or joint analysis for clinical endpoints and biomarkers will be initiated post SAC, based on the results ot the statistical analysis. The dataset to support this analysis and the analysis plan will be described in a separate document.

13. BIOMARKER ANALYSES

Exploratory biomarker analysis will take place at the final SAC.

13.1. Primary Biomarker Analyses

13.1.1. Endpoint / Variables

The following endpoints will be collected and presented in the outputs. Only systemic endpoints will be presented at baseline for IA2.

13.1.1.1. Systemic:

13.1.1.1.1. Fibrosis markers:

- Pro-C3
- C3M
- Pro-C6
- C6M
- PINP
- C1M (Note: Cohort 1 assay used antibody generated using mouse hybridoma cell line (old C1M kit). Cohort 2 assay used recombinant detection antibody, these will be summarised and plotted separately)
- COMP
- PIIINP
- HA
- TIMP-1

13.1.1.1.2. Derived fibrosis markers:

- Pro-C3/C3M (ratio)
- Pro-C6/C6M (ratio)
- PINP/C1M (ratio) (Note for C1M, Cohort 1 assay used antibody generated using mouse hybridoma cell line (old C1M kit). Cohort 2 assay used recombinant detection antibody, these will be summarised and plotted separately)
- Enhanced Liver Fibrosis (ELF) test (a linear combination of hyaluronic acid (HA), amino-terminal propeptide of type III Procollagen (PIIINP, a measurement of collagen III synthesis) and tissue inhibitor of metalloproteinase 1 (TIMP-1) in serum, this derived score will be provided by the vendor

13.1.1.1.3. Inflammation markers:

- CRP
- IL-6
- MCP-1 (Rename MCP-1 as CCL2 for displays)
- CCL-18

13.1.1.1.4. Vascular markers:

- vWF
- VEGF
- sVCAM-1
- NT-ProBNP

13.1.1.2. Skin Histology

- Alpha Smooth Muscle Actin (αSMA)

(Note: During the review process of Alpha SMA samples, some samples were found to have insufficient tissue due to shallow biopsies. Summaries, stats analysis and plots exclude those insufficient samples. Additional summary and plots will be produced on the full data (including both the sufficient and insufficient samples.)

13.1.1.3. Skin Gene expression RNA Sequencing:

13.1.1.3.1. Individual Genes of Interest:

- Inflammation genes: CCL2, CCL18, MS4A4A
- Fibrosis genes: THBS1, COMP
- PD marker at the site of action: SOCS3
- Target expression in skin: OSM, OSMR

13.1.1.3.2. Derived Gene:

- 2-gene SSc skin biomarker: 2GSSc (See Section 16.6.6 for derivation)

13.1.1.3.3. Gene Set Variation Analysis (GSVA) Score

GSVA (Hanzelmann, 2013) assesses the relative enrichment of a gene set of interest across all samples and generates an enrichment score for each gene set per individual sample. The algorithm will first calculate expression-level statistic for each gene using all the provided samples' gene expression distribution and subsequently rank the genes. Based on the expression-level statistic, the algorithm will then assess if the genes in the gene sets of interest are more likely to be enriched at either end of the ranking. The input of GSVA will be the rlog normalized and transformed expression matrix and the output of GSVA will be enrichment scores bound between 1 and -1 for each individual sample.

13.1.1.3.4. Disease signature

A broad set of public microarray datasets were used to create a systemic sclerosis gene signature in skin consisting of 251 individual genes, some of which are up-regulated and some of which are down-regulated in SSc skin compared to healthy skin (see Appendix 13 and eLNB reference number N76598-1 Section 2.1 and Section 3.1). The systemic sclerosis gene signature will be quantified using GSVA score.

- Individual Gene Sets: 209 Upregulated Genes and 42 Downregulated Genes
- Disease Signature: GSVA Scores (Upregulated and Downregulated)

13.1.1.3.5. Lung Fibrosis Signature

A broad set of public microarray datasets were used to create a lung fibrosis signature consisting of 42 individual genes. These genes can be detected in the skin and therefore lung fibrosis gene dysregulation can be evaluated in the skin biopsies. The lung fibrosis signature will be quantified using GSVA score. (see Appendix 13 and eLNB reference number N76598-1 Section 2.4 and Section 3.4).

13.1.1.3.6. Cell Module Signatures

The aim of the cell modules is to assess the effect of GSK2330811 on different cell-types and to compare the effect of GSK2330811 with the published tocilizumab data. The cell modules consist of three gene sets derived from Khanna, 2016b: Fibrosis (Table S3), M1-Macrophage (Table S7) and M2-Macrophage (Table S8). Cell module signatures will be quantified using GSVA score. (see Appendix 13)

- Individual Gene Sets: 37 Fibrosis Genes, 32 M1-Macrophage Genes and 31 M2-Macrophage Genes.
- Cell Module Signatures: GSVA Scores (Fibrosis, M1-Macrophage and M2-Macrophage)

13.1.2. Summary Measure

Interim 2:

The baseline values will be summarised without treatment groups using the safety population presenting summary statistics assuming a skewed distribution for the systemic markers. A scatter plot of the raw baseline values will be presented alongside the geometric mean ± standard error.

The Spearman's and Pearson's correlations of the baseline values transformed using log base 10, will be calculated and presented for each combination of endpoints. The correlations will also be presented as scatter plots for each pair of endpoints. Where both the correlations are >-0.3 and <0.3 the correlation will be suppressed from the outputs.

Final analysis

Standard summaries at each planned timepoint will be used for biomarker endpoints assuming a skewed distribution. The ratio of the post-baseline to baseline values and fold change (geometric ratio <1 then fold change is -1/geometric ratio otherwise fold change is geometric ratio) will also be summarised.

Systemic biomarkers will be summarised and presented using a log 10 scale while the histology and gene sets will be summarised and presented using a log 2 scale. 2GSSc skin biomarker and GSVA Scores will be summarised and presented on linear scale.

Line plots of the unadjusted geometric means ± standard error for log transformed data and unadjusted means ± standard error for linear data will be presented by treatment group at each visit. Individual participant plots of the raw values will be presented by treatment group and individual plot lines are differentiated by MMF use at Day 1 (solid

line denote subjects on mycophenolate at day 1 and dashed line denote subjects not in mycophenolate at day 1). Information on positive autoantibodies is added to the subject ids in the legend as per Section 6.1.

13.1.3. Population of Interest

For Interim 2 the summaries will be based on the "Safety" population.

For other reporting efforts, the primary biomarker analyses will be based on the "Per Protocol" analysis population, unless otherwise specified.

13.1.4. Strategy for Intercurrent (Post-Randomization) Events

Biomarker analysis will not account for intercurrent events (i.e. will adopt a 'while on treatment' strategy).

13.1.5. Statistical Analyses / Methods

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

The endpoints / variables defined in Section 13.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Longitudinal model
The ratio to baseline for the following systemic biomarkers will be analysed using a Bayesian MMRM analysis using the log transformed data including only the placebo and GSK2330811 300mg arms:

- Pro-C3
- Pro-C6
- PINP
- ELF
- COMP
- PIIINP
- IL-6
- MCP-1 (Rename MCP-1 as CCL2 for displays)
- CCL-18

Non-informative priors will be used in these analyses, specifically the prior for the regression coefficient will be normally distributed with mean 0 and a variance of 10^6.The variance-covariance matrix for the within subject error across the visits will use an inverse-Wishart prior distribution, consisting of the identity matrix and the degrees of freedom will be the number of visits included in the model.

The models will be adjusted for the following covariates: MMF use at day 1, baseline value, treatment, visit, treatment by visit and baseline by visit interactions.

The change from baseline within each treatment group and the difference in the change from baseline across the treatment groups (GSK2330811 300mg – placebo) will be calculated and are back transformed to give the ratio to baseline and the ratio of the change relative to placebo respectively.

Posterior medians and equal tailed 95% credible intervals will be presented. In addition, the probability the ratios are <1 and fold changes (Posterior Medians, as ratio < 1 then fold change is -1/ratio otherwise fold change is ratio) will also be calculated. The line plot of the adjusted posterior medians ± credible intervals at each visit will be presented.

ANCOVA

The ratio to baseline of log transformed and change from baseline of linear data for the following skin histology and gene expression mRNA sequencing endpoints will be analysed using a Bayesian ANCOVA analysis including only the placebo and GSK2330811 300mg arms:

- Alpha SMA (Excluding Insufficient samples)
- COMP
- CCL2
- 2GSSc
- Disease Signatures - GSVA Scores (Upregulated and Downregulated)
- Lung Fibrosis Signature - GSVA Score
- Cell Modular Signatures - GSVA Scores (Fibrosis, M1-Macrophage and M2-Macrophage)

Non-informative priors will be used in these analyses, specifically the prior for the regression coefficient will be normally distributed with mean 0 and a variance of 10^6. The prior for the variance parameter will be an inverse-gamma (shape=0.001, scale=0.001).

The models will be adjusted for the following covariates: MMF use at day 1, baseline value and treatment.

Nature of Data	Output Presentation
Log Transformation	• The change from baseline and difference in the treatment groups (GSK2330811 300mg – placebo) will be back transformed to give ratio to baseline and ratio of the change relative to placebo respectively. • Posterior medians, equal tailed 95% credible intervals, probability that ratios < 1 and fold change (i.e., Posterior Medians, as ratio < 1 then fold change is -1/ratio otherwise fold change is ratio) will be presented.
Linear	• Change from baseline and the difference in the treatment groups (GSK2330811 300mg – placebo) will be calculated. • Posterior medians and equal tailed 95% credible intervals will be presented. Except for Downregulated GSVA score, the probability that difference < 0 will be calculated. For Downregulated GSVA score, the probability > 0 will be calculated.

The plot of the adjusted posterior medians ± credible intervals along with individual ratio to baseline or change from baseline values based on the endpoints will be presented.

Joint model

In addition to the Bayesian MMRM analysis, the ratio to baseline or change from baseline based on the endpoints for the following four key biomarkers will be modelled using a multivariate Bayesian analysis including only the placebo and GSK2330811 300mg arms:

- Alpha SMA (Excluding Insufficient samples)
- CCL2 gene assessed from the skin sample through RNA sequencing
- PIIINP assessed from the serum sample
- 2GSSc

Non-informative priors will be used for all parameters. The variance-covariance matrix for the within subject error across the endpoints will use an inverse-Wishart prior distribution consisting of the identity matrix and 4 degrees of freedom.

The model will be adjusted for endpoint (allows each endpoint to have their own intercept), treatment by endpoint interaction term, MMF use at day 1 by endpoint interaction, and baseline by endpoint interaction term. If the model does not converge, the covariate for MMF use will be removed from the model.

Missing baseline covariates will be modelled as part of the MCMC sampling prior to fitting the joint model, using non-informative priors. For example, if b_i is the baseline of the ith endpoint then $b_i \sim N(\theta_i, \delta_i)$ where $\theta_i \sim N(0, sd=100)$ and $\delta_i \sim iGamma(shape=0.1, scale=0.1)$.

For modelling purposes, the log transformed endpoints will be back transformed for the presentation of results. Fold change will also be presented for only log transformed endpoints, posterior medians as, ratio < 1 then fold change is -1/ratio otherwise fold change is ratio.

Heat Plots

Heat plots will be produced for the gene expression endpoints contributing to a gene signature using fold change from baseline. Fold change in Placebo, GSK2330811 100mg and GSK2330811 300 mg at day 85 will be presented in three columns using the 3-fold change cut off. Plot colour scales from blue to white to red scale, values above 3 or below -3 fold change will all be presented using the same colour.

Heat plots are produced for each individual gene from Disease Signature, Lung Fibrosis signature and Cell module signatures as mentioned in Section 13.1.1.3. Within each signature, genes are ordered based on 'Ward' clustering algorithm.

For further reference, heat plot with dendogram for full gene panel contributing to the different signatures will be produced and saved in Refdata folder.

Additional Post SAC transcriptomics analysis will be conducted and the details will be documented in a separate analysis plan.

13.1.5.1. Model Checking & Diagnostics

As an initial model fit 100,000 MCMC samples will be generated with a thin of 10, providing 10,000 samples to be used for the estimate of the posterior distribution. A burn-in of 5,000 samples will be used. Starting values for the parameters will be based on the mode of the prior distributions.

The following list of convergence diagnostics will be applied for each parameter (diagnostic checking outputs will be stored in the refdata folder in HARP in the relevant reporting effort):

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to the simulation. The number of samples generated, and/or the thinning may be increased to reduce the ratio of the MCSE/SD as deemed necessary.
- Trace plots of samples versus the simulation index will be visually inspected to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.
- Autocorrelation plots will be visually inspected to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).
- Density plots of the posterior for the model parameters will be plotted (should be smooth and with a single hump).

If the model is not deemed to have converged the following actions will be taken in the order described below:

- Increasing the number of MCMC samples and/or the thinning will be explored. The blocking of the parameters will be considered.

- For the joint model:

    - The variance of the parameters used to model the baseline data may be considered as fixed, based on the observed variance of the parameter rather than using $\delta_i \sim$iGamma(shape=0.1, scale=0.1).

    - The endpoint with the most missing data will be removed from the model and the joint model carried out on the remaining 3 endpoints.

- For the MMRM model:

    - If missing data at the post-treatment visits are causing the non-convergence, these visits will be removed and details included in a footnote.

- Removal of covariates will be considered, starting with MMF use at day1, then the baseline by visit interaction (if applicable).

After which if the model still does not converge, the model results will not be presented.

13.2. Exploratory Biomarker Analyses

13.2.1. Mechanistic Haematology

Note that the exploratory endpoints that are categorised as 'blood biomarkers related to mechanisms of anaemia and thrombocytopenia' in the protocol are categorised as 'Group 2 – Mechanistic Haematology/chemistry' in Section 7.2. Reporting of these parameters will use the same outputs as other Haematology/ chemistry but will only occur at the end of the study. See Appendix 12. No statistical analysis will be performed on these endpoints. These displays will use the 'Safety' population unless otherwise specified.

14. EFFICACY ANALYSES

Exploratory biomarker analysis will take place at the final SAC.

14.1. Exploratory Efficacy Analyses

14.1.1. Endpoint / Variables

The analyses of clinical disease assessments (preliminary assessment of efficacy in Systemic Sclerosis) will be based on the Per Protocol population, unless otherwise specified. They will consist of the following endpoints:

- mRSS
- HAQ-DI
- SHAQ VAS scales
- PhGA
- PtGA
- CRISS (derived – non-parametric summaries)
- Laboratory FVC (L) – (Note: impact of treatment on the rate of change will be inferred from the Figures)
- % predicted laboratory FVC
- Weekly Home FVC (L) – (Note: impact of treatment on the rate of change will be inferred from the Figures)

14.1.2. Summary Measure

Summary statistics for all endpoints listed in Section 14.1.1 will be presented by visit and for the change from baseline at each visit. Line plots of unadjusted means ± standard error at each visit and individual participant plots of the raw values will be presented by treatment groups and individual plot lines are differentiated by MMF use at Day 1 (solid line denote subjects on mycophenolate at day 1 and dashed line denote subjects not in mycophenolate at day 1). Information on positive autoantibodies is added to the subject ids in the legend as per Section 6.1.

14.1.3. Population of Interest

The efficacy analyses will be based on the "Per Protocol" analysis population, unless otherwise specified.

14.1.4. Strategy for Intercurrent (Post-Randomization) Events

Exploratory efficacy analysis will not account for intercurrent events (i.e. will adopt a 'while on treatment' strategy).

14.1.5. Statistical Analyses / Methods

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

The endpoints / variables defined in Section 14.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Longitudinal model

Longitudinal Bayesian model as specified in Section 13.1.5 will be fitted for the change from baseline in the following endpoints:

- mRSS
- HAQ-DI
- Laboratory FVC (L)

The difference in the differences from baseline will be calculated across the treatment groups (GSK2330811 300mg – placebo).

Posterior means and equal tailed 95% credible intervals will be presented. In addition, except for Laboratory FVC, the probability the differences are <0 will be calculated and for Laboratory FVC, differences are >0 will be calculated. The line plots of the adjusted posterior mean change from baseline ± credible intervals at each visit will be presented.

Non-Parametric Analysis

The CRISS endpoint is not expected to be normally distributed and so will be analysed using Bayesian non-parametric techniques including only placebo and GSK2330811 300mg arms.

Observed data from two groups are assumed to come from an underlying latent normal distributions with unit variance. Observations from these two latent normal distributions are generated from the truncated normal distributions in such a way to maintain the ordinality of the data. The parameter of interest is difference in the two latent means, δ. Prior distribution of δ, will be Cauchy distribution with shape parameter 0.5 and scale parameter $1/\sqrt{2}$. To obtain the posterior distribution for δ, analysis will follow the algorithm advocated by van Doorn, 2020.

Probability difference > 0 will be presented.

Boxplots of the predicted probability of improvement from baseline in the CRISS endpoints at day 85 and day 197 will be presented by treatment group.

Correlation Analysis

In addition, correlation analysis will be performed at Day 85 for set of endpoints listed below. The correlation will be presented as scatter plots of endpoints for each of the treatment groups, including the Pearson correlation coefficient. For ratios, correlations will use the log transformed data while the plot will present the untransformed data with the appropriate axis presented on the log scale.

- For each combination of change or ratio of key biomarkers
- Clinical endpoints vs biomarker endpoints for change or ratio (Following table lists the pair of endpoints to be plotted).

Endpoint 1	Endpoint 2	
		Ratio/Change
FVC (Change)	1. CCL18 (Serum) 2. Pro-C6 (Serum)	Ratio
	3. Disease Signature - GSVA Score (Upregulated and Downregulated) 4. Lung Fibrosis Signature - GSVA Score 5. Cell Module Signature - GSVA Score (Fibrosis, M1-Macrophage and M2-Macrophage)	Change
mRSS (Change)	1. Alpha SMA (Excluding Insufficient samples) 2. COMP (Skin) 3. CCL2 (Skin) 4. PIIINP (Serum)	Ratio
	5. 2GSSc Skin Biomarker 6. Disease Signature - GSVA Score (Upregulated and Downregulated) 7. Cell Module Signature - GSVA Score (Fibrosis, M1-Macrophage and M2-Macrophage)	Change
Baseline OSM (Skin)	1. Alpha SMA (Excluding Insufficient samples) 2. CCL2 (Skin) 3. PIIINP (Serum)	Ratio
	4. 2GSSc Skin Biomarker 5. mRSS	Change

Model checking and diagnostics will be carried out as described in Section 13.1.5.1.

15. REFERENCES

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16. APPENDICES

16.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

16.1.1. Exclusions from Per Protocol Population

A participant meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Participant did not receive at least 4 doses of study treatment
02	Placebo participant received active treatment
03	Participant did not participate in at least one post-dose assessment
04[1]	Participant excluded on basis of final review of inclusion/exclusion criteria
05[1]	Participant excluded on basis of final review of the prohibited medication use
[1] Note: Data reviewed and decisions regarding exclusions from the Per Protocol population will be documented in the electronic trial master file.	

16.2. Appendix 2: Schedule of Activities

16.2.1. Protocol Defined Schedule of Activities

The following SOA tables are taken from protocol amendment 4 and are included in the RAP for convenience.

Note that baseline ECG is a triplicate measurement; see Appendix 6.

16.2.1.1. 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	

16.2.1.2. Treatment period 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
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.

16.3. Appendix 3: Assessment Windows

Following visit windows are applied for early withdrawal and unscheduled visits. The target day is the planned analysis timepoint and windows have been constructed with limits approximately equally spaced between visits. If more than one values within analysis timepoint with equal distance from the target day then average will be used.

Table A:

Domain	Analysis Window		Analysis Timepoint
	Beginning Timepoint	Ending Timepoint	
All	Day 1	Day 1	Day 1
Vital Signs, Standard Haematology/Clinical Chemistry	Day 8	Day 22	Day 15
	Day 23	Day 36	Day 29
	Day 37	Day 50	Day 43
	Day 51	Day 64	Day 57
	Day 65	Day 78	Day 71
	Day 79	Day 99	Day 85
	Day 100	Day 134	Day 113
	Day 135	Day 176	Day 155
	Day 177	> Day 197	Day 197
Additional Haematology, Urinalysis, Laboratory FVC, SHAQ-VAS, HAQ-DI, PhGA, PtGA and CRISS	Day 68	Day 99	Day 85
	Day 145	> Day 197	Day 197
Immature Reticulocyte Fraction	Day 37	Day 50	Day 43
	Day 68	Day 99	Day 85
	Day 145	> Day 197	Day 197
ECG	Day 8	Day 22	Day 15
	Day 50	Day 64	Day 57
Target Engagement (OSM)	Day 8	Day 22	Day 15
	Day 23	Day 43	Day 29
	Day 50	Day 64	Day 57
	Day 78	Day 92	Day 85
	Day 108	Day 120	Day 113
	Day 145	Day 165	Day 155
	Day 187	> Day 197	Day 197
Blood Biomarkers	Day 15	Day 43	Day 29
	Day 44	Day 71	Day 57
	Day 72	Day 99	Day 85
	Day 145	> Day 197	Day 197
CRP	Day 8	Day 22	Day 15
	Day 23	Day 43	Day 29
	Day 44	Day 71	Day 57

Domain	Analysis Window		Analysis Timepoint
	Beginning Timepoint	Ending Timepoint	
	Day 72	Day 99	Day 85
	Day 100	Day 127	Day 113
	Day 145	> Day 197	Day 197
mRSS	Day 43	Day 71	Day 57
	Day 72	Day 99	Day 85
	Day 145	> Day 197	Day 197
Skin Biopsy	Day 55	Day 99	Day 85
Home FVC [1] **(Target visit -/+ 3 days)**	Day 5	Day 11	Day 8
	Day 12	Day 18	Day 15
	…	…	…
	> Day 194		Day 197

[1] Steps for Home FVC Slotting

- Step 1: Select maximum value within a day.
- Step 2: After slotting, select the closest target day.
- Step 3: If more than one value within the analysis timepoint with equal distance from the target day, the 'average of maximum value' will be used.

For PK, planned assessments will be summarised, unscheduled assessments will be listed. PopPK and PK/PD modelling will use all available data and will use actual relative time, not planned relative time.

Note: Following assessment window followed for all SRT reporting.
For safety, planned assessments will be summarised. Unscheduled and early withdrawal visits are included following the visit slotting algorithm for worst case or CTCAE grade summaries and figures. If more than one visit slots to the same analysis timepoint, the 'worst' case will be included in the summary and figure.

Table B:

Analysis Set / Domain	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
Safety/ Haematology	The target day is the planned analysis timepoint. The windows have been constructed with limits approximately equally spaced between visits	Days less than 0		Screening
		Day 1	Day 1	Day 1
		Day 2	Day 22	Day 15
		Day 23	Day 36	Day 29
		Day 37	Day 50	Day 43
		Day 51	Day 64	Day 57
		Day 65	Day 78	Day 71
		Day 79	Day 99	Day 85
		Day 100	Day 134	Day 113
		Day 135	Day 176	Day 155
		Day 177	Day 209	Day 197

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

16.4.1. Study Phases

In general, assessments and events will be classified according to the time of occurrence relative to study treatment start date. Specific rules for Concomitant Medications and Adverse Events are specified in the section below.

Treatment Phase	Definition
Pre-Treatment	Date < Study Treatment Start
On-Treatment	Study Treatment Start ≤ Date ≤ Study Treatment Stop Date +28 days
Follow up	Study Treatment Stop Date +28 days < Date

16.4.1.1. Study Phases for Concomitant Medication

Non-systemic sclerosis medications taken prior to and not ongoing at the screening visit were not captured for this study.

Concomitant Systemic sclerosis medications and systemic sclerosis medication history (prior treatments) are captured separately in the eCRF and reported separately.

16.5. Appendix 5: Data Display Standards & Handling Conventions

16.5.1. Reporting Process

<table>
<tr><th colspan="2">Reporting Process</th></tr>
<tr><td colspan="2">Software</td></tr>
<tr><td colspan="2">• The currently supported versions of SAS software will be used.</td></tr>
<tr><td colspan="2">Reporting Area</td></tr>
<tr><td>HARP Server</td><td>: \\uk1salx00175.corpnet2.com</td></tr>
<tr><td>HARP Areas</td><td>Compound: GSK2330811
Study: MID201247
Reporting efforts: internal_nn , Final where nn = number of each reporting effort, following HARP standard. The planned identity of each ‘internal’ reporting effort is shown in the table below:
<table>
<tr><th>Reporting effort (RE) name in RAP</th><th>Type</th><th>HARP folder / RE name</th></tr>
<tr><td>SRT1</td><td>Pre-programming/ dry run</td><td>srt_01</td></tr>
<tr><td>SRT1</td><td>Final</td><td>srt_02</td></tr>
<tr><td>DEC</td><td>Dry run</td><td>data_look_01</td></tr>
<tr><td>DEC</td><td>Final</td><td>safety_02</td></tr>
<tr><td>SRT2</td><td>Pre-programming/ dry run</td><td>data_look_02</td></tr>
<tr><td>SRT2</td><td>Final</td><td>srt_03</td></tr>
<tr><td>IA1</td><td>Pre-programming/ dry run</td><td>data_look_02</td></tr>
<tr><td>IA1</td><td>Final</td><td>safety_03</td></tr>
<tr><td>SRT3</td><td>Pre-programming/ dry run</td><td>data_look_03</td></tr>
<tr><td>SRT3</td><td>Final</td><td>srt_04</td></tr>
<tr><td>IA2</td><td>Pre-programming/ dry run</td><td>data_look_03</td></tr>
<tr><td>IA2</td><td>Final</td><td>safety_04</td></tr>
<tr><td>SRT4</td><td>Pre-programming/ dry run</td><td>data_look_04</td></tr>
<tr><td>SRT4</td><td>Final</td><td>srt_05</td></tr>
<tr><td>SRT5</td><td>Final</td><td>srt_06</td></tr>
<tr><td>SRT6</td><td>Final</td><td>srt_07</td></tr>
<tr><td>Adhoc DRC</td><td>Final</td><td>safety_05</td></tr>
<tr><td>SRT7</td><td>Final</td><td>srt_08</td></tr>
<tr><td>SAC</td><td>Pre-programming/ dry run</td><td>data_look_04</td></tr>
<tr><td>SAC</td><td>Final</td><td>Final</td></tr>
</table>
Note: SRTs or DRCs may be called on an ad-hoc basis which will affect the numbering in the table above. An up-to-date list of this mapping will be maintained by S&P during study conduct and the table above will be updated prior to the final reporting effort.</td></tr>
<tr><td>QC Spreadsheet</td><td>For each reporting effort will be located:
: \\uk1salx00175.corpnet2.com</td></tr>
</table>

Reporting Process	
	\arenv\arwork\gsk2330811\mid201247\ *[reporting effort]*\documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for tables at IA2 and Adhoc DRC and final reporting efforts.	

16.5.2. Reporting Standards

Reporting Standards
General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data will be reported according to the actual treatment the participant received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's. • Dates will be reported in the format DDMMMCCYY e.g. 01Jan2020 unless otherwise stated.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to randomisation will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
  • Include reference lines at '1' for all change from baseline and at '0' for all ratio to baseline plots.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings. Visits outside the defined assessment windows specified in Appendix 3 (Table A) will be included in listings but omitted from Figures, summaries and statistical analyses.

Unscheduled Visits
• Unscheduled visits will be slotted as specified in Appendix 3 Table A. • For SRT reporting only, Unscheduled visits will not be included in summary tables apart from

Reporting Standards	
any that derive 'maximum change' / 'worst-case' and CTCAE grade summaries, which will use unscheduled results. Assessment windows for the unscheduled visits for the CTCAE grade summaries are specified in Appendix 3 Table B. This will not be included in Figures where 'visit' is used on the axis, with the exception of the worst case CTCAE plots.	
Descriptive Summary Statistics	
Continuous Data (normally distributed)	Refer to IDSL Statistical Principle 6.06.1
Descriptive Summary Statistics (Skewed data)	N, n, geometric mean, standard deviation (SD) of logged data, between geometric coefficient of variation (CVb (%)), median, minimum and maximum will be reported. Log base e data: CVb (%) = √ (exp(SD^2) - 1) * 100 [NOTE: SD = SD of log base 'e' transformed data] Log base 2 data: CVb (%) = √ (exp($\log_e$(2)^2 SD^2) - 1) * 100 [NOTE: SD = SD of log base 2 transformed data] Log base 10 data: CVb (%) = √ (exp($\log_e$(10)^2 SD^2) - 1) * 100 [NOTE: SD = SD of log base 10 transformed data]
Descriptive Summary Statistics (Non-parametric data)	N, median, interquartile range (IQR), minimum, maximum
Categorical Data	N, n, frequency, %. N = the number of participants from the relevant analysis population for the group or sub group. n = the number of participants counted for the summary statistic.
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	No pharmacokinetic parameters will be summarised in this study, they will be produced for each participant from the population PK model and the typical value of model parameters is considered the appropriate summary.
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13. • For individual line plots, subjects on MMF at day 1 will be represented with a solid line and subjects not on MMF represented with a dashed line. The auto-antibody status of the subject will be given in the legend as per Section 6.1.	

16.5.3. Reporting Standards for Pharmacokinetics

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 16.9.1 Pharmacokinetic / Pharmacodynamic Dataset Specification
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 16.9.1 Pharmacokinetic / Pharmacodynamic Dataset Specification
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	Highest Concentration – Measured concentration in post dose till the time of nadir. Steady State – Measured concentration before the last administered dose.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

16.6. Appendix 6: Derived and Transformed Data

16.6.1. General

Multiple Measurements at One Analysis Time Point
• Where multiple assessments are made, the mean of replicate assessments at any given time point will be used as the value for that time point. This derived mean will be reported in the listing in addition to the individual assessments. • If there are two values within a time window the value closest to the target day for that window will be used (with the exception of the worst case summaries for parameters detailed in Section 16.3 for SRT outputs, where the worst case would be used). If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomisation date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Date ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Actual Relative Time

• Calculated as the time in days or fraction of a day before or after first dose
  • This will be calculated relative to exposure date and time for both pre- and post- dose assessments where relevant.
  • This provides an alternative to 'Study Day' with a meaningful value of 0 and is of benefit for profile plots showing results before and after dosing.

16.6.2. Study Population

Treatment Compliance
Total number of doses received and number of doses withheld are summarised for treatment compliance. Number of doses withheld will be calculated only for subjects who attended the study visit and dose was withheld, but will not include the subjects who missed dosing visits.
Exposure
Duration of exposure for the treatment phase will be calculated based upon the following formula. If a subject has at least 28 days of information after their last dose: *Duration of exposure in days = treatment stop date – treatment start date + 29* If a subject withdraws from the study or dies with less than 28 days of information after their last dose: *Duration of exposure in days = Date of withdrawal or death – treatment start date +1*

This assumes patients are exposed for a 28-day period post-dosing, in-line with the half-life of GSK2330811.

Demographics

Age

- Only birth year is captured on the eCRF, therefore GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  - The missing date and month will be imputed as '30th June'.
- Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)

- Calculated as Weight (kg) /Height (m)2

Disease Specific

Time from onset of the first non-Raynaud's phenomenon manifestation and Raynaud's phenomenon manifestation

Time in months calculated as date of first screening visit from onset of the first non-Raynaud's phenomenon manifestation.

Partial dates will be imputed as follows:

- Any subject with a missing day will have this imputed as day '01'.
- Any subject with a missing date and month will have this imputed as '1st January'.

Time in months will be rounded up to the nearest whole month for each subject before being summarised.

Baseline Autoantibody

Numeric results of RNA Polymerase III Antibody – Standard will be classified as,

Positive, if numeric values ≥20 and Negative, if numeric values <20.

DLCO

During study set-up, the Respiratory Function eCRF screen was set up to collect the screening DLCO (uncorrected for Hb) and DLCO (corrected for Hb) values in mL/min/mmHg. However, part way through the study, the team became aware that these results were being reported locally in different units (in some cases different than the units required per the eCRF), and some sites did not convert the values to the required eCRF units. A note to file in the eTMF documents the corrective and preventative actions.

DLCO summary tables will present data using ML/MIN/MMHG and therefore data collected using unit MMOL/MIN/KPA will be transformed using the following formula:

$$\text{ML/MIN/MMHG} = \text{MMOL/MIN/KPA} \times 2.987.$$

Based on information from data management (documented in the note to file) sites collected DLCO using the following units:

Site id	Unit
PPD	ML/MIN/MMHG
	ML/MIN/MMHG
	ML/MIN/MMHG
	ML/MIN/MMHG
	ML/MIN/MMHG
	ML/MIN/MMHG
	ML/MIN/MMHG
	ML/MIN/MMHG
	MMOL/MIN/KPA
	MMOL/MIN/KPA
	MMOL/MIN/KPA
	MMOL/MIN/KPA

	PPD	MMOL/MIN/KPA	
		MMOL/MIN/KPA	
		ML/MIN/MMHG	
		ML/MIN/MMHG	

16.6.3. Efficacy

Efficacy

CRISS Composite response index in dcSSc

CRISS is calculated in a two-step process (formula and text from Khanna, (2016)) and detailed in the section below.

There are two post-baseline assessments of CRISS. Each will use the initial baseline so that, for example, if a participant has a scleroderma renal crisis in the first CRISS period between baseline and week 12, they will receive a value of 0 for both the first CRISS period (week 12) and the second CRISS period (week 28) except for item (b). For item (b) participants will be classified based on their FVC at the current visit FVC regardless of their classification at previous assessments.

Step 1:
Participants who develop new or worsening cardiopulmonary and/or renal involvement due to systemic sclerosis are considered as not improved (irrespective of improvement in other core items) and assigned a probability of improving equal to 0.0. Specifically, if a subject develops any of the following:

a) New scleroderma renal crisis[1]
b) Decline in FVC % predicted >= 15% (relative to baseline), HRCT to confirm ILD (if previous HRCT of chest did not show ILD) and FVC < 80% of predicted[2][3]
c) New onset of left ventricular failure (defined as left ventricular ejection fraction <= 45%) requiring treatment [1] [2]
d) New onset of PAH on right-sided heart catheterization [1] requiring treatment [1] [2]

Notes:
1: Treating physician's judgement, is recorded directly in eCRF, details in SRM.
2: Attributable to systemic sclerosis
3: The three components of item b (FVC % predicted decline, absolute level of FVC % predicted and HRCT to confirm ILD) are recorded in the eCRF and will be derived by programming. Note that a historic diagnosis of ILD will be recorded in a different variable to one made during the study.

Items a) c) and d) are captured as part of the eCRF. Item b) the % predicted FVC criteria (>=15% declined from baseline and <80% at relevant visit) will be derived programmatically. HRCT is captured as part of the eCRF and is requested as required and at the discretion of the investigator.

- If the participant has a HRCT confirming ILD at or prior to the visit (including day 1 and screening period or historical diagnosis) they will be considered to have confirmed ILD. Then the % predicted FVC results would be used to assess if they meet part b) of step 1.
- If the participant does not have a HRCT confirming ILD or has had a HRCT without presence of ILD then they would not meet the criteria for part b) of step 1.

Step 2:
For the remaining subjects who do not have a step 1 event a participant's probability of improving is calculated. Step 2 involves computing the predicted probability of improving using the following equation (equation to derive predicted probabilities from a logistic regression model):

Efficacy

$$\frac{exp\left[-5.54 - 0.81 * \Delta_{MRSS} + 0.21 * \Delta_{FVC\%} - 0.40 * \Delta_{Pt-glob} - 0.44 * \Delta_{MD-glob} - 3.41 * \Delta_{HAQ-DI}\right]}{1 + exp\left[-5.54 - 0.81 * \Delta_{MRSS} + 0.21 * \Delta_{FVC\%} - 0.40 * \Delta_{Pt-glob} - 0.44 * \Delta_{MD-glob} - 3.41 * \Delta_{HAQ-DI}\right]}$$

If a participant does not have a step 1 event and is missing any component of step 2, their CRISS predicted probability of improving will be set to missing.

Where:

Name on formula:	Definition used for 201247 at a given timepoint	Variable name in protocol:
ΔMRSS	Change in mRSS total score from baseline to timepoint	mRSS total score change from baseline
ΔFVC%	Change in clinic FVC % predicted from baseline to timepoint	% predicted FVC change from baseline
ΔPt-glob	Change in patient global assessment from baseline to timepoint	PtGA change from baseline
ΔMD-glob	Change in physician global assessment from baseline to timepoint	PhGA change from baseline
ΔHAQ-DI	Change in HAQ-DI from baseline to timepoint	HAQ-DI change from baseline (note that the HAQ-DI is a sub-component of the SHAQ)

SHAQ and HAQ-DI

The Scleroderma Health Assessment Questionnaire (SHAQ) is comprised of:

- The Health Assessment Questionnaire Disability Index (HAQ-DI) (calculated based on 21 items across 8 domains) that assess the impact of illness affecting the ability to function in daily life.
- 6 individual Visual Analogue Scales assess severity of pain, disease severity and the impact of each of the folllowing symptoms on activities of daily living:
  - Intestinal Problems
  - Breathing Problems
  - Raynaud's Phenomenon
  - Finger Ulcers
- The SHAQ will be completed by the participant during scheduled clinic visits and before any other assessments.
- For display purpose use the following terminologies to represent the SHAQ-VAS Questionarrie
  - CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

HAQ-DI

There are 8 sections: *dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities*. There are 2 or 3 questions for each section. Scoring within each section is from 0 (CCI [redacted]) to 3 (CCI [redacted]). For each section the score given to that section is the worst score within the section, i.e. if one question is scored 1 and another 2, then the score for that section is 2.

In addition, if an aide or devise is used or if help is required from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made. When there are

Efficacy

no aids or devices or help indicated for a category, the category's score is not modified. Where the aid or device for each section is:

HAQ-DI Category	Companion AIDS OR DEVICES item
DRESSING & GROOMING	Devices used for dressing (button hook, zipper pull, long handled shoe horn etc.)
ARISING	Special or built up chair
EATING	Built up or special utensils
WALKING	Cane, walker, crutches, wheelchair
HYGIENE	Raised toilet seat, bathtub seat, bathtub bar, long handled appliances in bathroom
REACH	Long handled appliances for reach
GRIP	Jar opener (for jars previously opened).

If a response to a component question within a section is left blank, then the score for that section is determined by the remaining completed question(s) within the section.

The HAQ-DI is calculated from the taking the 8 scores of the 8 sections are summed and divided by 8. If one section is not completed by a participant, then the summed score would be divided by 7. At least 6 sections must be non-missing for the HAQ-DI to be calculated, else the HAQ-DI is set to missing.

VAS scales

VAS scales will be converted to a 0-3 scale before contributing to the SHAQ. The scaled VAS score will be calculated as: Scaled score = score*0.03. Scaled VAS scores will be presented in outputs.

Lab & Home FVC

Where multiple assessments are taken, the largest of the non-missing values will be used in the analysis.

16.6.4. Safety

ECG Parameters

RR Interval

- If RR interval (msec) is not provided directly, then RR can be derived as:
  (1/HR)/1000(i.e. 1 / heart rate where the heart rate is taken as part of the ECG)
- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. QTcF or QTcB values entered by the site will always be presented in output.
- IF RR interval (msec) is provided (or can be derived from HR) then missing QTcB and/or QTcF will be derived as:

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 decimal places: '< x' becomes x – 0.01
  - Example 2: 1 decimal places: '> x' becomes x + 0.1
  - Example 3: 0 decimal places: '< x' becomes x – 1

- Reticulocyte Production Index (RPI) will be calculated, by GSK S&P, as:

RPI = Reticulocyte Count [%] x [Hematocrit [%] / 45] x 1/RMT

To use the formula above Hematocrit and Reticulocyte Count must be converted from the SI unit (proportion) to a percentage by multiplying by 100 (note that the GSK code describes reticulocyte count as a percentage even though it is a proportion).

Where Normal Hematocrit [%] = 45 and RMT (reticulocyte maturation time) is found from the table below:

Haematocrit	RMT
>=40%	1.0
30% to 39.9%	1.5
20% to 29.9%	2.0
<20%	2.5

- Corrected calcium will be calculated, by GSK S&P as:

*Corrected Calcium [mmol/L] = Serum Calcium [mmol/L] + 0.02 * (40[g/L] – Serum Albumin[g/L])*

Where Normal Serum Albumin = 40 [g/L]

- eGFR (estimated Glomerular Filtration Rate) will be calculated by GSK S&P at all timepoints, this will also be provided directly by the vendor at screening. The GSK calculated value at screening will be used as primary for reporting (e.g. will be used as baseline if appropriate).
- The calculation will be as follows:

*SI Results MDRD (GFR) (ml/min/1.73m^2) = (175 * (PD9S3/88.4) $^{-1.154}$) * (Age $^{-0.203}$ * Race * Sex)*
Where PD9S3 = Serum Creatinine (UMOL/L),
Race = 1.212 for Black & 1.000 for other, Sex = 1.00 for males and 0.742 for females.

16.6.5. Pharmacodynamic

Derived Parameters for Serum Level of OSM

% Target Engagement (TE%)

TE (%) = 100*(1- [Free OSM/Baseline Free OSM])
Note: predicted value will be presented, this will be derived by CPMS

16.6.6. Biomarkers

Derived Parameters for Fibrosis and Histology

ELF

The ELF test will be provided by the vendors using on the ADVIA Centaur system. For reference, here is the formula as specified in the laboratory manual (Rev. C, 2015-01).

Calculation of Results

The ELF score can be calculated manually or by the ADVIA Centaur systems. For detailed information about how the system calculates results, refer to the system operating instructions.

Note The auto-calculation feature is only available for the ADVIA Centaur XPT system, for the ADVIA Centaur XP system software version 7.0 or higher, and for the ADVIA Centaur CP system software version 6.0 or higher. For the ADVIA Centaur system, and earlier versions of the ADVIA Centaur XP and ADVIA Centaur CP systems, calculate the ELF score manually.

To calculate the ELF score manually for the ADVIA Centaur and ADVIA Centaur XP systems, first obtain results for the ADVIA Centaur HA, PIIINP, and TIMP-1 assays, and then use the following equation to calculate the ELF score:

$$\text{ELF score} = 2.278 + 0.851 \ln(C_{HA}) + 0.751 \ln(C_{PIIINP}) + 0.394 \ln(C_{TIMP\text{-}1})$$

Concentrations (C) of each of the constituents are in ng/mL.

To calculate the ELF score manually for the ADVIA Centaur CP system, first obtain results for the HA, PIIINP, and TIMP-1 assays on the ADVIA Centaur CP system, and then use the following equation to calculate the ELF score:

$$\text{ELF score} = 2.494 + 0.846 \ln(C_{HA}) + 0.735 \ln(C_{PIIINP}) + 0.391 \ln(C_{TIMP\text{-}1})$$

Concentrations (C) of each of the constituents are in ng/mL.

Note The ELF score is a unitless numerical value.

Alpha SMA

αSMA= αSMA Area (μm²)/(Dermis Area).

2GSSc Skin Biomarker

2GSSc = -27.6844 + (4.46*(Baseline THBS1)) + (5.31*ΔMS4A4A) + (4.96*ΔTHBS1)

Where, ΔMS4A4A and ΔTHBS1 are change from baselines and Baseline THBS1 is baseline value of THBS1 on log 2 scale

General

If biomarker values are below the lower limit of quanitification, data will be imputed as half the lower limit of quantification (LLQ).

If biomarkers are above the upper limit of quantification, data will be imputed as for lab data, where the number of decimal places in the observed values will be used to determine how much to add in order to impute the corresponding numeric value:

- Example 1: 2 decimal places: '> x' becomes x + 0.01
- Example 2: 1 decimal places: '> x' becomes x + 0.1
- Example 3: 0 decimal places: '> x' becomes x + 1

16.7. Appendix 7: Reporting Standards for Missing Data

16.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as completion of all assessments on Day 197(Week 28). • In cohort 1 non-evaluable participants will be replaced. • In cohort 2 withdrawn participants are not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and Figures, unless otherwise specified.

16.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a “blank” in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as reported.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

16.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4. ○ Missing Stop Day: Last day of the month will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent

Element	Reporting Detail
	on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

16.7.2.2. Handling of Missing Data for Statistical Analysis

For the joint model, missing baseline data will be modelled as part of the MCMC sampling, no post baseline data will be imputed. For all other models, missing data will not be imputed.

16.7.2.3. Handling of Missing Data for PK Analysis

GSK standards for handling missing PK data will be applied to all PK outputs.

16.8. Appendix 8: Values of Potential Clinical Importance

16.8.1. Laboratory Values - Haematology

Haematology parameters will use CTCAE grades (CTCAE criteria, V4.03: June 14, 2010) to highlight important results based on laboratory value only (i.e. no clinical judgement will be applied). CTCAE grades will replace the category of "values of potential clinical importance" for haematology parameters, see table below for reference.

Parameter	CTCAE v4.03 Term for Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin	Anemia	Hemoglobin (Hgb) <LLN - 100 g/L	Hgb <100 - 80g/L	Hgb <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Haemoglobin	Hemoglobin increased	Increase in >0 - 20 g/L above ULN or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN or above baseline if baseline is above ULN	Increase in >40 g/L above ULN or above baseline if baseline is above ULN	-
Haptoglobin	Haptoglobin decreased	<LLN	-	-	-
Lymphocyte count	Lymphocyte count decreased	<LLN - 0.8 GI/L	<0.8 - 0.5 GI/L	<0.5 - 0.2 GI/L	<0.2 GI/L
Lymphocyte count	Lymphocyte count increased	-	>4 - 20 GI/L	>20 GI/L	-
Neutrophil count	Neutrophil count decreased	<LLN - 1.5 GI/L	<1.5 - 1.0 GI/L	<1.0 - 0.5 GI/L	<0.5 GI/L
Platelet count	Platelet count decreased	<LLN - 75.0 GI/L	<75.0 - 50.0 GI/L	<50.0 - 25.0 GI/L	<25.0 GI/L
White blood cell count	Leukocytosis	-	-	>100 GI/L	Clinical manifestations of leucostasis; urgent intervention indicated
White blood cell count	White blood cell decreased	<LLN - 3.0 GI/L	<3.0 - 2.0 GI/L	<2.0 - 1.0 GI/L	<1.0 GI/Lp

16.8.2. Laboratory Values – Chemistry and Liver

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	G/L		30	
Calcium	mmol/L		2	2.75
Creatinine	µmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

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

16.8.3. ECG

ECG Parameter	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		>530
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60
'QTc' (corrected QT interval) may be recorded as QTcF, QTcB or another method documented in the SI code list. These limits should be applied to both QTcF, QTcB (which will be primary output variables) and alternative QTc methods (which will be listed where relevant)			

16.8.4. Vital Signs

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

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range
		An increase or decrease from baseline of the following magnitude
Systolic Blood Pressure	mmHg	≥ 40
Diastolic Blood Pressure	mmHg	≥ 20
Heart Rate	bpm	≥ 30

16.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

The details of the PopPK model are specified in Appendix 10 (PopPK/PD model). The first intent is to simultaneously estimate the parameters of the PopPK/PD model, using total GSK2330811 and Total OSM data. If a sequential modelling approach (i.e. PopPK model and PK/PD separately) is required, the principles and details specified in Appendix 10 will apply to the PopPK model. Appendix 10

16.9.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

Pharmacokinetic / Pharmacodynamic Dataset Specification

NONMEM dataset 1: PK/PD

- To support both the PK and the PK/PD analyses a NONMEM dataset will be generated
- The population PKPD dataset will be used for both the PK and the PK/PD analysis selecting the rows which apply.
- It will be a comma delimited text file, named *<"NM.GSK2330811*.201247*.PKPD.v1.csv">*.
- This file will include events of dosing or concentration as rows, with the variables in the table below as columns. Rows will be in increasing order of unique subject identification number; and all events in the same subject must be consecutive and in chronological order, ending with the last concentration event (i.e. dosing events that occur after the last quantifiable concentration in a subject will not be included in the data file).
- All plasma and blister fluid GSK2330811 and PD (free and total OSM in blister and serum) will be included (i.e. all scheduled and unscheduled visits).
- Non-numerical concentration values (such as missing samples, not assayed samples or non-reportable samples) will not be included. Subjects with non-quantifiable concentration values will be included.

Name	Implicit Unit	Description	Derivation	Format
ID	-	Unique subject identification number	PKCNC.SUBJID for concentration events and EXPOSURE.SUBJID for dosing events.	Numeric
TRFD	H	Event time from first dose	(PKCNC.PCSTDM – MSTONE.MSTSTDM)/3600 for PK concentration events. Similarly for PD concentration events and EXPOSURE.EXSTDM – MSTONE.MSTSTDM)/3600 for dosing events. Rounded to 2 decimal places.	Numeric
DV	PK: ng/mL PD: pg/ml for OSM	For concentration events: plasma and blister fluid concentration of GSK2330811, OSM free and total in serum and blister. For dosing events: 0	PKCNC.PCSTRESN for PK concentration events (similarly for PD concentration events). "0" for dosing events. "0" for non-quantifiable concentrations BIOMARK.BIORESN for BITESTCD=	Numeric

Name	Implicit Unit	Description	Derivation	Format
			CONCTSZ (Normal Activity) for OSM	
BQL		Below limit of quantification concentrations	1 for non-quantifiable concentrations, 0 otherwise Note: LLQ=100ng/mL for GSK2330811; LLQ=1.4pg/mL for Free and Total OSM	numeric
AMT	mg	For dosing events: dose of GSK2330811. For concentration events: 0	For dosing events (i.e. EVID=1): 0 for subjects on Placebo and dose for subjects on GSK2330811. For concentration events (i.e. EVID=0) AMT=0.	numeric
MDV	-	For concentration events: 0 For non-quantifiable concentration values: 0. For dosing events: 1	Hard coded as description (1 if data is from EXPOSURE; 0 if PKCNC.PCSTRESN or PD is not missing; 0 if PCSTRESN is missing and PCORRES is not missing, i.e. non-quantifiable sample).	Numeric
EVID		For DOSE events: 1, for concentration events: 0		
CMT	-	Compartment: For dosing events 1, for PK concentration events: 2. For PD concentration events: 4 and 5.	1 in records with LABL= “DOSE”. 2 in records with LABL= “PK”. 4 in records with LABL= ”PD” and ASSAY_NAME=”Free Oncostatin M”. 5 in records with LABL= ”PD” and ASSAY_NAME=”Total Oncostatin M” .	Numeric
NOMT	H	Planned PK sample time relative to dose For dosing events: 0 For pre-dose concentration events: 0	Extract numeric part of PKCNC.PTM (or format PTMNUM). Similarly for PD. For dosing events = "0"	Numeric
DAY	-	Study day	PKCNC.PCACTSDY for concentration events (similarly for PD) and EXPOSURE.EXACTSDY for dosing events.	Numeric
VIS	-	Visit number	PKCNC.VISITNUM (visit sequence number) for PK events (similarly for PD) and EXPOSURE.VISITNUM for dosing events.	Numeric
DOSE	mg	Dose of GSK2330811 in mg (for all events)	AMT added to all records	Numeric
STUD	-	Numeric part of study identifier (i.e. 201247)	201247 for all records	Numeric
BASELINE	Same unit of DV for each	0 if LABL_NAME=”PK” and ”DOSE”, baseline		Numeric

Name	Implicit Unit	Description	Derivation	Format
	ASSAY_NAME	otherwise		
SEX		Subject gender	1 for males and 2 for females	Numeric
WT	kg	Body weight at baseline visit	VITALS.WEIGHT at baseline visit.	Numeric
BMI	kg/m2	Body mass index at baseline visit	VITALS.WEIGHT/(VITALS.HEIGHT/100)^2	Numeric
HT	cm	Height at baseline visit	VITALS.HEIGHT	Numeric
DATE	-	Date of event	For dosing events, EXPOSURE.EXSTDT. For PK events, PKCNC.PCSTDT. Similarly for PD.	DD/MM/YYYY
TIME	-	Clock time of event	For dosing events, EXPOSURE.EXSTTM. For PK events, PKCNC.PCSTTM. Similarly for PD.	HH:MM
LLQ	-	Lower Limit of Quantitation	.	Numeric
FLAG		1 to 7	1 in records with LABL= “DOSE”. 2 in records with LABL= ”PK” and MATRIX_NAME=”Plasma”. 3 in records with LABL= ”PK” and MATRIX_NAME=”Blister Fluid”. 4 in records with LABL= ”PD” and ASSAY_NAME=”Free Oncostatin M” and MATRIX_NAME=”serum”. 5 in records with LABL= ”PD” and ASSAY_NAME=”Total Oncostatin M” and MATRIX_NAME=”Serum”. 6 in records with LABL= ”PD” and ASSAY_NAME=”Free Oncostatin M” and MATRIX_NAME=”Blister Fluid”. 7 in records with LABL= ”PD” and ASSAY_NAME=”Total Oncostatin M” and MATRIX_NAME=”Blister Fluid”.	numeric
REGIMEN		Regimen sort order		numeric
COHORT		Cohort sort order		numeric
LABL_NAME	-	Record label	VARCHAR2(32) Maximum 32 characters (numeric or text), Record identifier: In dosing records: “DOSE” In PK concentration records “PK”	varchar

Name	Implicit Unit	Description	Derivation	Format
			in PD concentration records "PD"	
ASSAY_NAME	-	Used assay	In records with LABL="DOSE" and "PK", use "PK_assay" In records with LABL="PD" use the appropriate assay: "OSM free etc"	varchar
MATRIX_NAME		Used matrix (i.e. "plasma", "serum", "blister")	.	varchar
MRSS		mRSS score		numeric

Dataset 2: PK/PD and Haematology

The dataset will include exposure, total OSM, Platelets (PLT), Red Blood Cells (RBC), Reticulocytes (RET), Haemoglobin (Hb), Immature reticulocyte fraction, Reticulocytes (percentage/ratio), erytropoyetin (EPO) and thrombopoietin (TPO)

- An additional dataset will be generated to support graphical analyses for haematology biomarkers
- It will be a comma delimited text file, named eda-gsk2330811-201247-pkhaem.csv.
- This file will include time of visits as rows, with the variables in the table below as columns. Rows will be in increasing order of unique subject identification number; and all events in the same subject must be consecutive and in chronological order.
- if any variable is missing at a certain time, assign NA.
- All scheduled and unscheduled visits will be included for plasma GSK2330811, serum Total OSM and haematology (Platelets, Red Blood Cells, Reticulocytes, Haemoglobin, Immature reticulocyte fraction, Reticulocytes (percentage/ratio), EPO, TPO). Only central labs readings will be included.
- Non-numerical concentration values (such as missing samples, not assayed samples or non-reportable samples) will not be included. Subjects with non-quantifiable concentration values will be included.

Pseudocode:

Select SUBJID, ELTMSTN, PCSTRESN, PCACTSDY, VISITNUM, PCSTDT from PKCNC where PKCNC.PCSPEC='Plasma'. There should be one record per subject per visit.

Rename NOMT=ELTMSTN, DAY= PCACTSDY, DATE=PCSTDT

Select SUBJID, ATRGDY, BISTRESN, BIACTDY, VISITNUM, BIDT from BIOMARKER where BICATCD in ('TOSM') and AVISIT is not 'DAY 1'. There should be one record per subject per visit.

Mutate ATRTGDY= ATRGDY-1

Rename NOMT=ATRTGDY, DAY=BIACTDY, DATE=BIDT

Select SUBJID, AVISIT, LBSTRESN, LBACTDY, VISITNUM, BIDT (please verify if this is the date information) from LABHAEM where LBTESTCD in ('PLT_BLC', HB_BLC, RBC_BLC, RETIC_BLC, IRF_BLQ, RETIC_BLQ, EPO_PLC, THROMB_PLC)

Calculate NOMT as follow: if AVISIT='BASELINE' then NOMT=0 else NOMT=(numerical part of AVISIT). Drop AVISIT.
Rename DAY= LBACTDY, DATE=BIDT

Transpose records by SUBID, NOMT DAY,DATE,VISITNUM (var=LBSTRESN, id= LBTESTCD) so that there is one record per subject per visit. Each variable in LBTESTCD will be a column.

Join selected PKCNC and BIOMARKER records by SUBJID, NOMT, DAY, DATE

Join with LABHAEM dataset by SUBJID, NOMT, DAY, DATE

Select SUBJID, and information on DOSE, SEX, WT, BMI, HT, REGIMEN and COHORT from appropriate dataset and Join by SUBJID

Name	Implicit Unit	Description	Derivation	Format
SUBJID	-	Unique subject identification number		Numeric
NOMT	h	Planned sample time relative to dose		Numeric
CONC	ng/mL	GSK2330811 plasma concentration	PKCNC.PCSTRESN where PKCNC.PCSPEC='Plasma' if PKCNC.PCSTRESC='NQ' then CONC=0 if >1 observation at same date/time, take the mean.	numeric
TOSM	pg/mL	Total OSM serum concentration	BIOMARK.BISTRESN where BICATCD in ('TOSM') and AVISIT is not 'DAY 1' if >1 observation at same date/time, take the mean.	
PLT	1E9/L	platelet count	LBSTRESN where LBTESTCD in ('PLT_BLC')	

Name	Implicit Unit	Description	Derivation	Format
HB	g/L	haemoglobin	LBSTRESN where LBTESTCD in ('HB_BLC')	
RBC	TI/L	red blood cells	LBSTRESN where LBTESTCD in ('RBC_BLC)	
RETIC	TI/L	reticulocytes	LBSTRESN where LBTESTCD in ('RETIC_BLC')	
IMRETF		immature reticulocyte fraction	LBSTRESN where LBTESTCD in ('IRF_BLQ')	
RETPR	ratio	reticulocyte (percentage/ratio)	LBSTRESN where LBTESTCD =' RETIC_BLQ'	
EPO		erithropoietin	in clinical chemistry lbtestcd="EPO_PLC".	
TPO	ng/L	thrombopoietin	LBSTRESN where LBTESTCD =' THROMB_PLC'	

Name	Implicit Unit	Description	Derivation	Format
DAY	-	Study day		Numeric
VISITNUM	-	Visit number		Numeric
DATE	-	Date of event		DD/MM/YYYY
DOSE	mg	Dose of GSK2330811 in mg		Numeric
SEX		Subject gender	1 for males and 2 for females	Numeric
WT	kg	Body weight at baseline visit	VITALS.WEIGHT at baseline visit.	Numeric
BMI	kg/m2	Body mass index at baseline visit	VITALS.WEIGHT/(VITALS.HEIGHT/100)^2	Numeric
HT	cm	Height at baseline visit	VITALS.HEIGHT at baseline	Numeric
REGIMEN		Regimen sort order		numeric
COHORT		Cohort sort order		numeric

Dataset 3: PK and Clinical efficacy and biomarkers

The dataset will include exposure-related parameters and clinical efficacy and biomarker endpoints. The dataset will be required after SAC, based on the results of the statistical analysis.

16.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Methodology

Concentration-time profiles of GSK2330811 in plasma and Total OSM in serum, will be analysed by population pharmacokinetic/pharmacodynamic (PopPK/PD) methods using a non-linear mixed-effects modelling approach.

The objective of this analysis is to develop population PK/PD models that characterize the concentration-time profile of GSK2330811 and total OSM following repeated subcutaneous administration of GSK2330811 in patients with dcSSc.

Concentration-time profiles of GSK2330811 in plasma and platlets and haemoglobin will be analysed by PK/PD methods using a non-linear mixed-effects modelling approach. All the available exposure haematology clinical data relative to GSK2330811 will be combined for the analysis. This pooled analysis will be performed as a separate analysis and reported separately.

Analysis of clinical endpoints and biomarkers could include exposure-response, longitudinal exposure-response and joint modelling. This analysis would be performed after SAC, based on the results of the statistical analysis.

16.10.1. Systems

The quantitative analysis will be performed using NONMEM (ICON Solutions) and PsN (Perl Speaks NONMEM) or another software platform deemed appropriate. Graphical displays and, if needed, modifications of the dataset will be produced using R (The R Foundation for Statistical Computing). The analysis will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline using the GSK modelling environment MAP (Model-based Analysis Platform) using the currently supported versions of all software packages.

16.10.2. Data Assembly

GSK Stats and Programming will generate the NONMEM input dataset, as detailed in Section 16.9.1.

16.10.3. Model Development

A population PK/PD model for SC single dose of GSK2330811 in healthy volunteers was developed [Reid J, 2018] and will be the starting point for the population PK/PD analysis.

Individual parameters (empirical Bayes estimates) will be derived applying the HV popPKPD model to the repeat dose in dcSSc dataset with the MAXEVAL=0 option, if $EST METHOD=1, or with the EONLY=1 option, if $EST METHOD=IMP. If the corresponding model diagnostics indicate that the HV popPKPD model is appropriate to represent the dcSSc PKPD data, then these individual parameters for the dcSSc population will be considered adequate to characterise the PK/PD.

If the parameter set of the HV popPKPD model applied to the dcSSc data set results in substantial bias or if a further exploration of the covariate effect in the dcSSc population is deemed necessary, the parameters of the HV popPKPD model will be re-estimated for the dcSSc PK/PD data alone and/or for a pooled HV (study 201246, study 208564 cohort 1) /dcSSc (study 201247) data set. If a pooled analysis is deemed necessary, it will be performed as a separate analysis and reported separately.

16.11. Appendix 11: Abbreviations & Trade Marks

16.11.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
AUC	Area under the (Concentration-Time) Curve
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRP	C-Reactive Protein
CRISS	Composite Response Index in diffuse cutaneous Systemic Sclerosis
CS	Clinical Statistics
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBF	Database Freeze
DBR	Database Release
dcSSc	Diffuse Cutaneous Systemic Sclerosis
DOB	Date of Birth
DP	Decimal Places
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ELF	Enhanced Liver Fibrosis
EPO	Erythropoietin
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HAQ-DI	Health Assessment Questionnaire Disability Index HAQ-DI
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
MMRM	Mixed Model Repeated Measures
mRSS	modified Rodnan skin score
OSM	Oncostatin M
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Friderica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate

Abbreviation	Description
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RSE	Relative standard error
SAC	Statistical Analysis Complete
SD	Standard Deviation
SE	Standard Error
SDTM	Study Data Tabulation Model
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TPO	Thrombopoietin

16.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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

16.12. Appendix 12: List of Data Displays

16.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.32	NA
Safety (incl. immunogenicity)	3.1 to 3.36	3.1 to 3.16
Pharmacokinetic	4.1	4.1 to 4.8
Population Pharmacokinetic (PopPK)	5.1 to 5.2	5.1 to 5.3
Pharmacodynamic	6.1 to 6.4	6.1 to 6.6
Pharmacokinetic / Pharmacodynamic	7.1 to 7.2	7.1 to 7.4
Biomarker	8.1 to 8.23	8.1 to 8.25
Exploratory Efficacy	9.1 to 9.22	9.1 to 9.23
Section	**Listings**	
ICH Listings	1 to 34	
Other Listings	35 to 51	

16.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays will be provided in a separate document.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln
Biomarker	BIO_Fn	BIO_Tn	BIO_Ln

NOTES:

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

16.12.3. Deliverables

Delivery [Priority] [1]	Description
SRT	Safety Review Team
DEC	Dose Escalation
DECX	Expanded Dose Escalation *[conditional on DEC decision].* Note that all outputs created for DEC will also be produced for DECX unless specified. Depending on the reason for expansion this RAP may be further developed for the DECX interim.
IA1	Interim Analysis 1 Statistical Analysis Complete ("Target Engagement" interim)

Delivery [Priority] [1]	Description
IA2	Interim Analysis 2 Statistical Analysis Complete ("Baseline biomarker" interim)
Adhoc DRC	Statistical Analysis Complete at request of the data review committee (DRC)
SAC	Final Statistical Analysis Complete

NOTES: Indicates priority (i.e. order) in which displays will be generated for the reporting effort, priority may not be specified

For interim analyses, not all outputs produced for the interim will automatically be shared in the meeting. For example, if it is not necessary to review individual level data then, although this may have been produced, it will not be reviewed by the DRC. Also, as described above, outputs from the preceding SRT may be shared at any interim but note that the data cut for the SRT may be at a different time than the data cut for the DEC and that SRT outputs may be produced from data that has not been cleaned by data management.

16.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition	Include Total Column	SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
1.3.	Safety	SD1	Summary of Treatment Status and Reason for Discontinuation of Study Treatment	Include Total Column	SAC
1.4.	Enrolled	NS1	Summary of Number of Subjects by Country and Centre ID	PLS Requirement	SAC
1.5.	Per Protocol	NS1	Summary of Number of Subjects by Country and Centre ID	PLS Requirement	SAC
Protocol Deviations					
1.6.	Safety	DV1	Summary of Important Protocol Deviations not Related to COVID-19		SAC
1.7.	Safety	DV1	Summary of Important Protocol Deviations Related to COVID-19		SAC
Populations Analysed					
1.8.	Screened	SP1	Summary of Study Populations		IA1, IA2, SAC
1.9.	Safety	SP2	Summary of the Exclusions from the Per Protocol Population	Include programmatical exclusions specified in Section 16.1.1.	SAC
Demography					
1.10.	Safety	DM1	Summary of Demographic Characteristics		IA1, IA2, Adhoc DRC, SAC
1.11.	Per Protocol	DM1	Summary of Demographic Characteristics	Only produce if per-protocol population is different from the safety population.	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.12.	Enrolled	DM11	Summary of Age Ranges		SAC
1.13.	Safety	DM6	Summary of Race and Racial Combination Details		IA2, Adhoc DRC, SAC
Disease characteristics					
1.14.	Safety	POP_T1	Summary of Systemic Sclerosis Disease History		IA1, IA2, SAC
1.15.	Safety	POP_T2	Summary of Systemic Sclerosis Medication History		IA1, IA2, SAC
1.16.	Safety	POP_T2	Summary of Concomitant Mycophenolate		IA1, IA2, SAC
1.17.	Safety	POP_T3	Summary of Historical Autoantibody Profile		IA1, IA2, SAC
1.18.	Safety	POP_T3	Summary of Baseline Autoantibody Profile		SAC
1.19.	Safety	EFF_T1	Summary of DLCO (mL/min/mmHg) at Screening	By treatment, Include corrected and uncorrected for Hb.	SAC
1.20.	Per Protocol	POP_T1	Summary of Systemic Sclerosis Disease History	As for Table 1.12. Only produce if per-protocol population is different from the safety population.	SAC
1.21.	Per Protocol	POP_T2	Summary of Systemic Sclerosis Medication History	As for Table 1.13. Only produce if per-protocol population is different from the safety population.	SAC
1.22.	Per Protocol	POP_T2	Summary of Concomitant Mycophenolate	As for Table 1.14. Only produce if per-protocol population is different from the safety population.	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.23.	Per Protocol	POP_T3	Summary of Baseline Autoantibody Profile	As for Table 1.16. Only produce if per-protocol population is different from the safety population.	SAC
1.24.	Per Protocol	EFF_T1	Summary of DLCO (mL/min/mmHg) at Screening	By treatment, Include corrected and uncorrected for Hb. Only produce if per-protocol population is different from the safety population.	SAC
1.25.	Per Protocol	POP_T4	Summary of Mycophenolate use at Day 1	If biomarker analysis will be done by safety population, use safety population here.	SAC
Concomitant Medications and Medical Conditions					
1.26.	Safety	MH1	Summary of Current/Past Medical Conditions other than Systemic Sclerosis		SAC
1.27.	Safety	CM8	Summary of Concomitant Medications by Ingredient and Ingredient Combinations		IA1, IA2, SAC
1.28.	Safety	SU1	Summary of Smoking History		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
1.29.	Safety	POP_T5	Summary of Treatment Compliance	Add footnotes: '[1] Includes subjects who attended the study visit and a dose was withheld, it does not include subjects who missed dosing visits.' 'Note: Percentages use n as denominator'.	SAC
1.30.	Per Protocol	POP_T5	Summary of Treatment Compliance	Add footnotes: '[1] Includes subjects who attended the study visit and a dose was withheld, it does not include subjects who missed dosing visits.' 'Note: Percentages use n as denominator'.Only produce if per-protocol population is different from the safety population.	SAC
1.31.	Safety	POP_T6	Summary of Exposure to Study Treatment		SAC
1.32.	Per Protocol	POP_T6	Summary of Exposure to Study Treatment	Only produce if per-protocol population is different from the safety population.	SAC

16.12.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
3.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term, by Treatment Phase	For IA1, don't present by phase and remove ', by Treatment Phase' from the title. Add a row to include number of participants contributing to treatment phase and use as denominator. Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	IA1, IA2, Adhoc DRC, SAC
3.2.	Safety	AE3	Summary of Common (>=5%) Adverse Events, by Treatment Phase	Add a row to include number of participants contributing to treatment phase and use as denominator. Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	SAC
3.3.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.4.	Safety	AE5A	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Intensity, by Treatment Phase	Add a row to include number of participants contributing to treatment	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.5.	Safety	AE1	Summary of Drug-Related Adverse Events, by Treatment Phase	phase and use as denominator. Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	SAC
3.6.	Safety	AE5A	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity, by Treatment Phase		SAC
3.7.	Safety	AE3	Summary of Non-Serious Drug-Related Adverse Events, by Treatment Phase		SAC
Serious AEs					
3.8.	Safety	AE1	Summary of Non-Fatal Serious Adverse Events, by System Organ Class, by Treatment Phase	Add a row to include number of participants contributing to treatment phase and use as denominator. Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	SAC
3.9.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class and Preferred Term, by Treatment Phase	For IA1, don't present by phase and remove ', by Treatment Phase' from the title. Add a row to include number of participants contributing to treatment phase and use as denominator. Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	IA1, IA2, SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.10.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.11.	Safety	AE3	Summary of Serious Drug-Related Adverse Events, by Treatment Phase	Add a row to include number of participants contributing to treatment phase and use as denominator.	SAC
3.12.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term, by Treatment Phase	Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	SAC
3.13.	Safety	AE3	Summary of Non-Fatal Drug-Related Serious Adverse Events, by Treatment Phase	Add a row to include number of participants contributing to treatment phase and use as denominator.	SAC
3.14.	Safety	AE3	Summary of Fatal Drug-Related Serious Adverse Events, by Treatment Phase	Add footnote 'Note: On treatment phase defined as period from first dose to last dose + 28 days. Follow up phase defined as period after last dose + 28 days.'	
Chemistry					
3.15.	Safety	LB1	Summary of Chemistry		IA1, IA2, SAC
3.16.	Safety	LB1	Summary of Change from Baseline in Chemistry		IA1, IA2, SAC
3.17.	Safety	LB1	Summary of Percentage Change from Baseline in Chemistry		IA1, IA2, SAC
3.18.	Safety	LB17	Summary of Worst-Case Chemistry Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		DEC, SAC
Haematology					

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.19.	Safety	SAFE_T1	Summary of Blinded Haematology	Blinded dataset. Page by cohort. By Parameter, this output should be produced for the blinded safety parameters (Table 3 in Section 3.1.1.2). These are: Platelet Count, Haemoglobin, Haematocrit, RBC count For SRTs, include date of the central lab data cut.	SRT, DEC
3.20.	Safety	SAFE_T1	Summary of Change from Baseline – Blinded Haematology	Blinded dataset. Page by cohort. By Parameter, this output should be produced for the blinded safety parameters Table 3 in Section 3.1.1.2). These are: Platelet Count, Haemoglobin, Haematocrit, RBC count For SRTs, include date of the central lab data cut.	SRT, DEC
3.21.	Safety	SAFE_T3	"[Blinded] Summary of Platelet Count and Anaemia Events by CTCAE Grade [and cohort]	By Parameter / event. Just Haemoglobin (anemia) and Platelet count decrease For SRT use 'Blinded' i.e. do not report treatment code but do report cohort (i.e. cohort 1 and cohort 2) For Interims and final do use treatment code, do not use cohort.	SRT IA1, IA2, Adhoc DRC, SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.22.	Safety	SAFE_T4	Summary of Haematological Limits Crossed During Study	Haemoglobin, report two events: <80 g/L (permanent discontinuation), <90g/L (repeat test) Platelets, report three events: <50 GI/L,(permanent discontinuation) >=50 GI/L & <75 GI/L (temporary discontinuation) and <100 GI/L (repeat test)	SAC
3.23.	Safety	LB1	Summary of Haematology	By parameter	IA1, IA2, Adhoc DRC, SAC
3.24.	Safety	LB1	Summary of Haematology Change from Baseline	By parameter	IA1, IA2, Adhoc DRC, SAC
3.25.	Safety	LB1	Summary of Percentage Change from Baseline in Haematology	By parameter	IA1, IA2, Adhoc DRC, SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.26.	Safety	LB16	Summary of Haematology Results by Maximum CTCAE Grade Increase Post-Baseline Relative to Baseline	Add Footnote: [1] CTCAE grade determined using laboratory values only as defined in V4.03: June 14, 2010 and does not take into account the clinical context. Note: Subjects are counted in Increase to Grade 1, 2, 3 and 4 by comparing the baseline grade to the maximum post baseline grade. Increase to Grades 1 to 4 is by adding number of subjects in Increase to Grade 1, 2, 3, and 4. Increase to Grades 2 to 4 is by adding number of subjects in Increase to Grade 2, 3 and 4. Increase to Grades 3 to 4 is by adding number of subjects in Increase to Grade 3 and 4."	IA1, IA2, Adhoc DRC, SAC
3.27.	Safety	SAFE_T5	Summary of Nadirs for Selected Haematology Parameters	Haematology parameter group 1 only. by parameter, treatment group. Do not produce for Reticulocytes (i.e. produce for Haemoglobin, Red Blood Cells, Platelets and Absolute Neutrophil Counts only). Footnote: "Nadir is the lowest post-baseline value of the parameter including local lab results. Haematology Group 1 Parameters: Haemoglobin, Red Blood Cells, Platelet Count and Absolute Neutrophil Counts."	IA1, IA2, Adhoc DRC, SAC
3.28.	Safety	SAFE_T5	Summary of Nadirs for Selected Haematology Parameters as Percent Change from Baseline		DEC, IA1, IA2, Adhoc DRC, SAC
3.29.	Safety	SAFE_T6	Summary of Days to Nadir of Selected Haematology Parameters		DEC, IA1, IA2, SAC
Urinalysis					
3.30.	Safety	SAFE_T7	Summary of Emergent Worst Case Urinalysis Results		IA1, IA2, SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ECG					
3.31.	Safety	EG1	Summary of ECG Findings		IA1, IA2, SAC
3.32.	Safety	EG2	Summary of ECG Values	"Note: If multiple assessments collected in any clinical visits then the mean of the multiple values within the assessments has been used in the summary."	IA1, IA2, SAC
3.33.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit		IA1, IA2, SAC
Vital Signs					
3.34.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit		IA1, IA2, SAC
3.35.	Safety	VS7	Summary of Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		IA1, IA2, SAC

16.12.6. Immunogenicity Tables (may be categorised under Safety in HARP folder structure / SAFIRE naming)

Immunogenicity: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Immunogenicity					
3.36.	Safety	IMM1	Summary of Positive Immunogenicity results	Add footnote: Note: The denominator for confirmed positive is the total number of subjects at that visit who have immunogenicity data available.	SAC

16.12.7. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
3.1.	Safety	AE10	Plot of Top 20 Adverse Events and Relative Risks	Top 20 AE by overall number of events. Add following footnote and use in programming rules: "Note: Top 20 Adverse Events by overall number of events displayed and the AE has to have at least 1 occurrence in the placebo group for relative risk to be calculated. Only AEs with calculated relative risk are displayed."	SAC
Chemistry					
3.2.	Safety	BIO_F2	Mean Profile for Chemistry Results by Treatment Group	For Haptoglobin, Ferritin, Vitamin B12 and Folate. Add footnote "Figure displays a subset of Chemistry parameters"	SAC
3.3.	Safety	BIO_F4	Subject Profiles for Chemistry Results by Treatment Group		SAC

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Haematology					
3.4.	SRT Safety	SAFE_F2	Minimum Value at Each Visit – Blinded Haematology	By Haematology parameter, this output should be produced for the blinded safety parameters (Table 3 in Section 3.1.1.2). These are: Platelet Count, Haemoglobin, Haematocrit, RBC count Show relevant CTCAE grades as reference lines on y axis. The relevant boundary is the highest-grade level that the lowest lab value is above (e.g. if the lowest values are just above grade 2, then show grade 2). Where grade depends on individual demographics (e.g. age, sex) show the highest boundary that applies to the analysis population.	SRT, DEC
3.5.	SRT Safety	SAFE_F2	Greatest Reduction from Baseline at Each Visit – Blinded Haematology	By Haematology parameter, this output should be produced for the blinded safety parameters (Table 3 in Section 3.1.1.2). These are: Platelet Count, Haemoglobin, Haematocrit, RBC count Scatter plot, one point per planned visit. Include 0 on y-axis	SRT, DEC

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.6.	Safety	201246/final/ Figure 3.1	Participant Profiles of Haematology by Treatment Group	By Haematology parameter, this output should be produced for the blinded safety parameters (Table 3 in Section 3.1.1.2) **with the exception of** Haematocrit. i.e. for: Platelet Count, Haemoglobin, RBC count Do not show grade 1 boundary. Show grade 2 boundary (or higher) as described for output 3.2 if any participant exceeds grade 1. X axis use 'Actual relative time' from dose. Show all observed values including unscheduled. Add footnote "Figure displays a subset of haematology parameters"	DEC[1], **IA1**[1], IA2[1]
3.7.	Safety	BIO_F4	Subject Profiles for Haematology by Treatment Group	By Haematology parameter. For SAC for Haematology parameter group 1, Red Cell Distribution Width and mean platelet volume. Use rules for CTCAE boundaries for Figure 3.7 X axis use 'Time (Days)' from dose. Show all observed values including unscheduled. Add footnote "Figure displays a subset of haematology parameters" Panel by treatment group	Adhoc DRC, SAC
3.8.	Safety	BIO_F4	Subject Profiles for Percentage Change from Baseline Haematology by Treatment Group		Adhoc DRC, SAC
3.9.	Safety	BIO_F2	Mean Profile for Haematology by Treatment Group	By Haematology parameter. For IA1 and IA2 for Haematology	**IA1**, IA2, Adhoc DRC, SAC

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.10.	Safety	BIO_F2	Mean Percentage Change from Baseline for Haematology by Treatment Group	parameter group 1. For SAC, Haematology parameter group 1, Red Cell Distribution Width and mean platelet volume. X axis shows visits with approximate temporal spacing Add footnote "Figure displays a subset of haematology parameters"	**IA1**, IA2, Adhoc DRC, SAC
3.11.	Safety	PK_F1	Scatter Plot of Platelet Nadir vs. Haemoglobin Nadir	Panel by treatment group and grouped by individual subjects X-axis Label: Platelet Nadirs Y-axis Label: Haemoglobin Nadirs	**SAC**
Hepatobiliary (Liver)					
3.12.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT		SAC
3.13.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin		SAC
3.14.	Safety	201246/final/ Figure 3.9	LFT Patient Profiles	Single plot combining the following parameters: ALT = Alanine Amino Transferase, AST = Aspartate Amino Transferase, Alk. Phos. = Alkaline Phosphatase,Total Bili. = Total Bilirubin	SAC
ECG					
3.15.	Safety	EG7	Empirical Distribution Function for Maximum Change from baseline in QTcF Interval	All treatments on one plot. Calculate maximum change from baseline.	SAC
3.16.	Safety	EG8	Distribution of QTcF Change by Visit and Treatment	Use the 0, 30, 60 thresholds following shell.	SAC

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Notes: 1: Individual figure(s) will be produced for interim but may not be shared. Justification: DRCs follow the principle of presenting summary data where possible to reduce the degree of unblinding, so this output will only be presented if necessary.					

16.12.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Plasma Concentration					
4.1.	PK	PKCT1	Summary of Plasma GSK2330811 Concentration-Time Data (ng/mL)	Add footnotes “ Note: No. of subjects with results below the lower limit of quantification, assigned 0 (LLQ=100 ng/mL). SD is set to missing if No. Imputed/n > 0.3 Samples from Day 14 – Day 84 are taken at trough (2 weeks after dosing).”	DEC, IA1, IA2, Adhoc DRC, SAC

16.12.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Plasma Concentration					
4.1.	PK	PKCF1P	Individual GSK2330811 Plasma Concentration-Time Plot by Subject (Linear and Semi-Log)	Footnote for all PK and PK/PD figures: Note: No. of subjects with results below the lower limit of quantification, assigned 0 (LLQ=100 ng/mL). Samples from Day 14 – Day 84 are taken at trough (2 weeks after dosing). Use actual time (days) as x axis (where days is a continuous variable)	DEC[1], SAC
4.2.	PK	PKCF1P	Individual GSK2330811 Plasma Concentration-Time Plot by Treatment (Linear and Semi-Log)	Use actual time (days) as x axis (where days is a continuous variable) [difference between this and 4.1 is that all profiles will be on one page for each treatment group] Note: No. of subjects with results below the lower limit of quantification, assigned 0 (LLQ=100 ng/mL). Samples from Day 14 – Day 84 are taken at trough (2 weeks after dosing).	IA1[1], IA2[1], Adhoc DRC, SAC
4.3.	PK	PKCF4	Mean (±SD) Plasma GSK2330811 Concentration-Time Plots by Treatment (Linear and Semi-log)	Use planned time (days) as x axis (where days is a continuous variable) Note: No. of subjects with results below the lower limit of quantification, assigned 0 (LLQ=100 ng/mL). Samples from Day 14 – Day 84 are taken at trough (2 weeks after dosing).	IA1, IA2, SAC
4.4.	PK	PKCF5	Median (Range) Plasma GSK2330811 Concentration-Time Plots by Treatment (Linear and Semi-log)		SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.5.	PK	201246/adhoc/ Figure 4.9	Mean (±SD) Plasma GSK2330811 Concentration-Time Plots **grouped** by Treatment (Linear and Semi-log)	As Figure 4.3 but on a single page, grouped by treatment. Add footnote Note: No. of subjects with results below the lower limit of quantification, assigned 0 (LLQ=100 ng/mL). Samples from Day 14 – Day 84 are taken at trough (2 weeks after dosing).	IA1, IA2, Adhoc DRC, SAC
4.6.	PK	PK_F1	Scatter Plot of Individual Measured Steady State Concentration vs Baseline Body Weight	Panel by treatment group and grouped by individual subjects. X-axis Label: Body Weight (kg) Y-axis Label: Measured Steady State Concentration (ng/mL)	Adhoc DRC, SAC
4.7.	PK	PK_F1	Scatter Plot of Individual Platelet Nadirs as Percentage Change from Baseline vs Measured Highest Concentration	Panel by treatment group and grouped by individual subjects. X-axis Label: Measure Highest Concentration (ng/mL) Y-axis Label: Percentage Change from Baseline of Platelet Nadirs	Adhoc DRC, SAC
4.8.	PK	PK_F1	Scatter Plot of Individual Hemoglobin Nadirs as Percentage Change from Baseline vs Measured Highest Concentration	Panel by treatment group and grouped by individual subjects. X-axis Label: Measure Highest Concentration (ng/mL) Y-axis Label: Percentage Change from Baseline of Hemoglobin Nadirs	SAC
Notes: 1: Individual figure(s) will be produced for interim but may not be shared with the study team. Justification: DRCs follow the principle of presenting summary data where possible to reduce the degree of unblinding, so this output will only be presented if necessary.					

16.12.10. Pharmacokinetic Population (PopPK) Tables

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PopPK					
5.1.	PK	NA	Summary of Derived Plasma GSK2330811 Pharmacokinetic Parameters from Population PK model	Produced by CPMS Note: this table will contain the parameters from the Population PK analysis (which already summarise all the subjects). It will NOT be a summary of the individual subject's parameters. Optional Footnote: Parameters estimated from study 201246 OR Parameters estimated from observed data and data from 201246.	**IA1**, SAC
5.2.	PK	NA	Predicted median (95%CI) vs Observed Mean (SE) plasma GSK2330811 concentration	Produced by CPMS	DEC, **IA1**, SAC

16.12.11. Pharmacokinetic Population (PopPK) Figures

Pharmacokinetic Population (POPPK): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PopPK					
5.1.	PK	NA	Predicted Median (95% **CI**) vs Mean (SE) of Plasma GSK2330811	Produced by CPMS At each dose level Footnote: CI = Confidence Interval	DEC, IA1, IA2, Adhoc DRC, SAC
5.2.	PK	NA	Predicted Median (95% **PI**) vs Individual Observed Values of GSK2330811	Produced by CPMS At each dose level Note: May not be shared with the study team at interim analyses. Footnote: PI = Prediction Interval	DEC[1], IA1[1] SAC
5.3.	PK	NA	Predicted Median (95% **PI**) vs Observed Range of GSK2330811	Produced by CPMS At each dose level Footnote: PI = Prediction Interval	DEC, IA1, IA2, Adhoc DRC, SAC
Notes: 1: Individual figure(s) will be produced for interim but may not be shared. Justification: DRCs follow the principle of presenting summary data where possible to reduce the degree of unblinding, so this output will only be presented if necessary.					

16.12.12. Pharmacodynamic Tables

Pharmacodynamic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serum OSM					
6.1.	Adhoc DRC: Safety SAC: Per Protocol	PD_T1	Summary of Log Transformed Serum Level of Free OSM (pg/mL)	Add number imputed, Add footnote: [1] No. of subjects with results below the lower limit of quantification, assigned to half of the lower limit of quantification **(LLQ = 1.45 pg/ml)**	Adhoc DRC, SAC
6.2.	IA1, IA2, Adhoc DRC: Safety SAC: Per Protocol	PD_T1	Summary of Log Transformed Serum Level of Total OSM (pg/mL)		IA1, IA2, Adhoc DRC, SAC
6.3.	Per Protocol	PD_T1	Summary of Ratio of Serum Level of Free OSM (pg/mL) to Baseline		SAC
6.4.	IA1, IA2: Safety SAC: Per Protocol	PD_T1	Summary of Ratio of Serum Level of Total OSM (pg/mL) to Baseline		IA1, IA2, SAC
Notes: Will be produced for interim but may not be shared due to small sample size being potentially unblinding.					

16.12.13. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serum OSM					
6.1.	IA1: Safety SAC: Per Protocol	PKCF1P	Individual Serum Level of Free OSM Concentration-Time Plot by Treatment (Linear and Semi-Log)	Add LLQ reference line Page by treatment Add Footnote to indicate amount of imputed data. Add footnote: [1] No. of subjects with results below the lower limit of quantification, assigned to half of the lower limit of quantification **(LLQ = 1.45 pg/ml)** Use actual time (days) as x axis (where days is a continuous variable) Note: May not be shared with study team at interim.	IA1[1], SAC
6.2.	IA1: Safety SAC: Per Protocol	PKCF1P	Individual Serum Level of Total OSM Concentration-Time Plot by Treatment (Linear and Semi-Log)	Add LLQ reference line. Conditionally add ULQ reference line Page by treatment Add footnote: [1] No. of subjects with results below the lower limit of quantification, assigned to half of the lower limit of quantification **(LLQ = 1.45 pg/ml)** Use actual time (days) as x axis (where days is a continuous variable) Note: May not be shared with study team at interim. Add Footnote to indicate amount of imputed data.	IA1[1], SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.3.	IA1, IA2: Safety SAC: Per Protocol	201246/adhoc/ Figure 5.19	Mean (±SD) Serum Level of Total OSM Concentration-Time Plots grouped by Treatment (Linear and Semi-log)	Add LLQ reference line Conditionally add ULQ reference line Use planned time (days) as x axis (where days is a continuous variable)	IA1, IA2, SAC
6.4.	IA1, IA2: Safety SAC: Per Protocol	201246/adhoc/ Figure 5.19	Median (Range) Serum Level of Total OSM Concentration-Time Plots grouped by Treatment (Linear and Semi-log)		IA1, IA2, SAC
Three panel PK/PD/Haematology plots					
6.5.	PK	201246/Final/ Figure 6.9	Median Plasma GSK2330811 Concentration, Median Serum Level of Total OSM Concentration and Median Platelet Count Over Time by Treatment Group	Page by treatment group Title of each panel to include endpoint and units, short form endpoint on y axis	SAC
6.6.	PP	201246/Final/ Figure 6.9 / 6.20	Median Serum Level of Total OSM Concentration, Median Haemoglobin and Median Reticulocytes by Treatment Group,		SAC

Notes:

1: Individual figure(s) will be produced for interim but may not be shared. Justification: DRCs follow the principle of presenting summary data where possible to reduce the degree of unblinding, so this output will only be presented if necessary.

16.12.14. Pharmacokinetic / Pharmacodynamic Tables

Pharmacokinetic / Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK/PD					
7.1.	IA1: Safety SAC: Per Protocol	NA	Parameters from Target Engagement PK/PD Model, [for specify model] Model.	CPMS to produce this output if PK/PD model is developed for the reporting effort.	IA1, SAC
7.2.	IA1: Safety SAC: Per Protocol	NA	Predicted median (95% CI) vs Mean (SE) Total OSM	CPMS to produce this	IA1, SAC

16.12.15. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK/PD					
7.1.	IA1, IA2, Adhoc DRC: Safety DEC, SAC: Per Protocol	NA	Predicted median (95% CI) vs Mean (SE) Total OSM	CPMS to produce this output	DEC, IA1, IA2, Adhoc DRC, SAC
7.2.	IA1: Safety DEC, SAC: Per Protocol	NA	Predicted target engagement over time	CPMS to produce this output	IA1, SAC
7.3.	IA1, IA2, Adhoc DRC: Safety DEC, SAC: Per Protocol	NA	Predicted median and (95% PI) vs Observed range of Total OSM	CPMS to produce this output	DEC, IA1, IA2, Adhoc DRC, SAC
7.4.	IA1: Safety DEC, SAC: Per Protocol	NA	Predicted median (95% PI) vs Observed Total OSM	CPMS to produce this output Note: Shows individual data points, might not be shown to study team at interim.	DEC, IA1, SAC

16.12.16. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Systemic biomarkers					
8.1	Safety	BIO_T1	Summary of Baseline Levels of Systemic Biomarkers	Baseline values only No treatment groups. Exclude C1M results using mouse hybridoma cell line as small sample size may be unblinding. Add footnote 'Note: C1M assay changed during the study. C1M results not presented for samples analysed using the old C1M (denoted C1M*) kit due to small sample size and potential unblinding. New C1M kit denoted as C1M+.	IA2
8.2	Per Protocol	BIO_T2	Summary of Systemic Biomarkers	By biomarker, by treatment ordered by endpoint type (Inflammation, Fibrosis, Vascular) Note: No. of subjects with results below the lower limit of quantification, assigned to half of the lower limit of quantification. Note: C1M assay changed during the study. Results using old kit denoted as C1M* and new kit denoted as C1M+. For only ratio to baseline table, add Fold change.	SAC
8.3	Per Protocol	BIO_T2	Summary of the Ratio to Baseline in Systemic Biomarkers		SAC

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.4	Per Protocol	BIO_T3	Analysis of Systemic Biomarkers	For endpoints as specified in Section 13.1.5.	SAC
Skin Histology biomarkers					
8.5	Per Protocol	BIO_T2	Summary of Alpha SMA Results	Include both sufficient and insufficient tissue samples	SAC
8.6	Per Protocol	BIO_T2	Summary of Alpha SMA Results Excluding Insufficient Tissue Samples		SAC
8.7	Per Protocol	BIO_T2	Summary of the Ratio to Baseline in Alpha SMA Results at Day 85 Excluding Insufficient Tissue Samples	Do not include Analysis visit column.	SAC
8.8	Per Protocol	BIO_T7	Analysis of the Ratio to Baseline in Alpha SMA Results at Day 85 Excluding Insufficient Tissue Samples	For endpoints as specified in Section 13.1.5.	SAC
Skin Gene Expression RNA Sequencing					
8.9	Per Protocol	BIO_T8	Summary of mRNA Gene Expression Results: Individual Genes of Interest	By gene, by treatment.	SAC
8.10	Per Protocol	BIO_T9	Summary of the Ratio to Baseline in mRNA Gene Expression Results at Day 85: Individual Genes of Interest		SAC
8.11	Per Protocol	BIO_T7	Analysis of the Ratio to Baseline in mRNA Gene Expression Results at Day 85: Individual Genes of Interest	For endpoints as specified in Section 13.1.5.	SAC
8.12	Per Protocol	BIO_T9	Summary of Ratio to Baseline in mRNA Gene Expression Results at Day 85: Disease Signature Genes	By gene sets, gene and treatment.	SAC
8.13	Per Protocol	BIO_T9	Summary of Ratio to Baseline in mRNA Gene Expression Results at Day 85: Lung Fibrosis Signature Genes	By gene, by treatment.	SAC
8.14	Per Protocol	BIO_T9	Summary of Ratio to Baseline in mRNA Gene Expression Results at Day 85: Cell Module Signature Genes	By gene sets, gene and, by treatment.	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.15	Per Protocol	BIO_T10	Summary of mRNA Gene Signature Results	Page by 2GSSc and GSVA scores. This include 2GSSc, Disease, Lung Fibrosis and Cell module Signatures.	SAC
8.16	Per Protocol	BIO_T10	Summary of the Change from Baseline in mRNA Gene Signature Results at Day 85		SAC
8.17	Per Protocol	BIO_T11	Analysis of the Change from Baseline in mRNA Gene Signature Results at Day 85		SAC
Joint model of key biomarkers					
8.18	Per Protocol	BIO_T5	Joint Model of Ratio to Baseline in Key Biomarkers at Day 85		SAC
8.19	Per Protocol	BIO_T6	Joint Probabilities for Key Biomarkers at Day 85		SAC
Correlation of Biomarkers					
8.20	Safety	BIO_T4	Correlation of Baseline Levels of Systemic Biomarkers	Baseline values only. No treatment groups. Exclude C1M results using mouse hybridoma cell line as small sample size may be unblinding. Add footnote 'Note: C1M assay changed during the study. C1M results not presented for samples analysed using the old C1M (denoted C1M*) kit due to small sample size and potential unblinding. New C1M kit denoted as C1M+.'	IA2
Mechanistic Haematology/ Chemistry					
8.21	Safety	SAFE_T1	Summary of Mechanistic Haematology/ Chemistry	Refer to Section 7.2 'Group 2' for	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.22	Safety	SAFE_T1	Summary of Change from Baseline in Mechanistic Haematology/ Chemistry	list of endpoints	SAC
8.23	Safety	SAFE_T1	Summary of Percentage Change from Baseline in Mechanistic Haematology/ Chemistry		SAC

16.12.17. Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Systemic biomarkers					
8.1	Safety	BIO_F1	Panel Plot of Baseline Levels of Systemic Biomarkers	Baseline values only, jittered scatter plot with superimposed geometric mean and standard error bars. Page 1 (2x4 plot): C3M, C6M, C1M, COMP, PINP, Pro-C3, Pro-C6 Page 2 (2x2 plot): HA, TIMP-1, PIIINP, ELF Page 3 (1x3 plot): Pro-C3/C3M, Pro-C6/C6M, PINP/C1M Page 4 (2x2 plot): CRP, IL-6, CCL2, CCL-18 (PARC1) Page 5 (2x2 plot): vWF, VEGF, sVCAM-1, NT-ProBNP Note: plot using order above. Exclude C1M results using mouse hybridoma cell line as small sample size may be unblinding. Add footnote 'Note: C1M assay changed during the study. C1M results not presented for samples analysed using the old C1M (denoted C1M*) kit due to small sample size and potential unblinding. New C1M kit denoted as C1M+	IA2

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.2	Per Protocol	BIO_F2	Line Plot of Systemic Biomarkers	Line plot of three treatment arms. page by biomarker, ordered by endpoint type (Inflammation, Fibrosis, Vascular) Y-axis presented to log base 10 scale. Note: No. of subjects with results below the lower limit of quantification, assigned to half of the lower limit of quantification. Note: C1M assay changed during the study. Results using old kit denoted as C1M* and new kit denoted as C1M+.	SAC
8.3	Per Protocol	BIO_F2	Line Plot of Analysis of Ratio to Baseline of Systemic Biomarkers	For endpoints as specified in Section 13.1.5.	SAC
8.4	Per Protocol	BIO_F4	Individual Subject Profiles of Systemic Biomarkers	Panel by treatment, page by biomarker, ordered by endpoint type (Inflammation, Fibrosis, Vascular) y-axis presented to log base 10 scale Note: No. of subjects with results below the lower limit of quantification, assigned to half of the lower limit of quantification. Note: C1M assay changed during the study. Results using old kit denoted as C1M* and new kit denoted as C1M+.	SAC
Histology biomarkers					
8.5	Per Protocol	BIO_F2	Line Plot of Alpha SMA Results	Include both sufficient and insufficient samples. Y-axis presented to log base 2 scale	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.6	Per Protocol	BIO_F2	Line Plot of Alpha SMA Results Excluding Insufficient Tissue Samples	Y-axis presented to log base 2 scale	SAC
8.7	Per Protocol	BIO_F6	Plot of Adjusted Ratio to Baseline of Alpha SMA Result vs Individual Ratio to Baseline Values at Day 85 Excluding Insufficient Tissue Samples		SAC
8.8	Per Protocol	BIO_F4	Individual Subject Profiles of Alpha SMA Results	Include both good and insufficient samples. Panel by treatment y-axis presented to log base 2 scale	SAC
8.9	Per Protocol	BIO_F4	Individual Subject Profiles of Alpha SMA Results Excluding Insufficient Tissue Samples	Panel by treatment y-axis presented to log base 2 scale	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Skin Gene Expression RNA Sequencing					
8.10	Per Protocol	BIO_F8	Line Plot of mRNA Gene Expression Results: Individual Genes of Interest	By Panel 1x2 Genes of Interest listed in Section 13.1.1.3.1(excluding derived gene) y-axis presented to log base 2 scale	SAC
8.11	Per Protocol	BIO_F6	Plots of Adjusted Ratio to Baseline vs Individual Ratio to Baseline Values in mRNA Gene Expression Results at Day 85: Individual Genes of Interest	By Panel 1x2. y-axis presented to log base 2 scale	SAC
8.12	Per Protocol	BIO_F4	Individual Subject Profiles of mRNA Gene Expression Results: Individual Genes of Interest	Panel by treatment and page by Genes of Interest listed in Section 13.1.1.3.1(excluding derived gene) y-axis presented to log base 2 scale	SAC
8.13	Per Protocol	BIO_F8	Line Plot of mRNA Gene Signature Results	Page by signature type. Page 1: 2GSSc Page 2 (Panel 1x3: Fibrosis, M1 and M2 score) Page 3 (Panel 1x2: Up/Downregulated disease signature score). Page 4 (Lung Fibrosis Score)	SAC
8.14	Per Protocol	BIO_F6	Plots of Adjusted Change from Baseline vs Individual Change from Baseline Values in mRNA Gene Signature Results at Day 85		SAC
8.15	Per Protocol	BIO_F4	Individual Subject Profiles of mRNA Expression Results: Disease Signature	Panel by treatment and page by Disease Signature	SAC
8.16	Per Protocol	BIO_F4	Individual Subject Profiles of mRNA Expression Results: Lung Fibrosis Signature	Panel by treatment	SAC
8.17	Per Protocol	BIO_F4	Individual Subject Profiles of mRNA Expression Results: Cell Module Signature	Panel by treatment and page by Cell module signature	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Correlation of Biomarkers					
8.18	Safety	BIO_F3	Correlation of Baseline Levels of Systemic Biomarkers	Baseline values only. No treatment groups. Exclude C1M results using mouse hybridoma cell line as small sample size may be unblinding. Add footnote 'Note: C1M assay changed during the study. C1M results not presented for samples analysed using the old C1M (denoted C1M*) kit due to small sample size and potential unblinding. New C1M kit denoted as C1M+.	IA2
Mechanistic Haematology/ Chemistry					
8.19	Safety	BIO_F2	Mean Profile for Mechanistic Haematology / Chemistry	Refer to Section 7.2 'Group 2' for list of tests. Add footnote "Figure displays a subset of haematology/chemistry parameters"	SAC
8.20	Safety	BIO_F2	Mean Percentage Change from Baseline Profile for Mechanistic Haematology / Chemistry		SAC
8.21	Safety	BIO_F4	Individual Subject Profiles for Mechanistic Haematology / Chemistry		SAC
Correlation Analyses of Key Biomarkers					
8.22	Per Protocol	EFF_F4	Correlation of Key Biomarkers at Day 85	Panel by treatment group and grouped by individual subjects.	SAC
Heat Plots of Skin Gene Expression RNA Sequencing					
8.23	Per Protocol	BIO_F7	Heat Plots of Fold Change from Baseline for mRNA Gene Expression Results: Disease Signatures	Pageby Up/Downregulated disease signature	SAC
8.24	Per Protocol	BIO_F7	Heat Plots of Fold Change from Baseline for mRNA Gene Expression Results: Lung Fibrosis Signature		SAC

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.25	Per Protocol	BIO_F7	Heat Plots of Fold Change from Baseline for mRNA Gene Expression Results: Cell Module Signatures	Pageby Fibrosis, M1-Macrophage and M2-Macrophage cell module signature	SAC

16.12.18. Exploratory Efficacy Tables

Exploratory Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
mRSS					
9.1	Per Protocol	EFF_T1	Summary of mRSS Total Score	By treatment, by visit	SAC
9.2	Per Protocol	EFF_T1	Summary of Change from Baseline in mRSS Total Score	By treatment, by visit	SAC
9.3	Per Protocol	EFF_T2	Analysis of Change from Baseline in mRSS Total Score	By treatment, by visit	SAC
FVC and % predicted FVC					
9.4	Per Protocol	EFF_T1	Summary of Laboratory FVC (L)	By treatment, by visit	SAC
9.5	Per Protocol	EFF_T1	Summary of Change from Baseline in Laboratory FVC (L)	By treatment, by visit	SAC
9.6	Per Protocol	EFF_T2	Analysis of Change from Baseline in Laboratory FVC (L)	By treatment, by visit	SAC
9.7	Per Protocol	EFF_T1	Summary of Laboratory Percent Predicted FVC	By treatment, by visit	SAC
9.8	Per Protocol	EFF_T1	Summary of Change from Baseline in Laboratory Percent Predicted FVC	By treatment, by visit	SAC
HAQ-DI and SHAQ VAS scales					
9.9	Per Protocol	EFF_T1	Summary of HAQ-DI	By treatment, by visit	SAC
9.10	Per Protocol	EFF_T1	Summary of Change from Baseline in HAQ-DI	By treatment, by visit	SAC
9.11	Per Protocol	EFF_T2	Analysis of Change from Baseline in HAQ-DI	By treatment, by visit	SAC
9.12	Per Protocol	EFF_T1	Summary of SHAQ VAS scales	By treatment, by visit, by VAS scale Add footnote: "Note: US English version of SHAQ-VAS Questionnaire presented in the output."	SAC
9.13	Per Protocol	EFF_T1	Summary of Change from Baseline in SHAQ VAS scales		SAC
PhGA and PtGA					
9.14	Per Protocol	EFF_T1	Summary of Physician Assessment of Global Disease Activity	By treatment, by visit	SAC

Exploratory Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
9.15	Per Protocol	EFF_T1	Summary of Change from Baseline in Physician Assessment of Global Disease Activity	By treatment, by visit	SAC
9.16	Per Protocol	EFF_T1	Summary of Patient Assessment of Global Disease Activity	By treatment, by visit	SAC
9.17	Per Protocol	EFF_T1	Summary of Change from Baseline in Patient Assessment of Global Disease Activity	By treatment, by visit	SAC
CRISS					
9.18	Per Protocol	EFF_T4	Summary of CRISS	Per visit (i.e. 12 weeks and follow up), by treatment. Use non-parametric summaries only	SAC
9.19	Per Protocol	EFF_T5	Summary of CRISS Step 1 Events		SAC
9.20	Per Protocol	EFF_T6	Analysis of CRISS		SAC
Home FVC					
9.21	Per Protocol	EFF_T1	Summary of Weekly Home FVC (L)		SAC
9.22	Per Protocol	EFF_T1	Summary of Change from Baseline in Weekly Home FVC (L)		SAC

16.12.19. Exploratory Efficacy Figures

Exploratory Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
mRSS					
9.1	Per Protocol	EFF_F1	Line Plot of mRSS Total Score	Unadjusted Mean ± SE	SAC
9.2	Per Protocol	EFF_F1	Line Plot of Analysis of Change from Baseline in mRSS Total Score	Posterior Mean ± SD	SAC
9.3	Per Protocol	BIO_F4	Individual Subject Profiles for mRSS Total Score	Panel by treatment	SAC
FVC and % predicted FVC					
9.4	Per Protocol	EFF_F1	Line Plot of Laboratory FVC (L)	Unadjusted Mean ± SE	SAC
9.5	Per Protocol	EFF_F1	Line Plot of Analysis of Change from Baseline in Laboratory FVC (L)	Posterior Mean ± SD	SAC
9.6	Per Protocol	BIO_F4	Individual Subject Profiles for Laboratory FVC (L)	Panel by treatment	SAC
9.7	Per Protocol	EFF_F1	Line Plot of Laboratory Percent Predicted FVC	Unadjusted Mean ± SE	SAC
9.8	Per Protocol	EFF_F1	Line Plot of Change from Baseline in Laboratory Percent Predicted FVC		SAC
#HAQ-DI and SHAQ VAS scales					
9.9	Per Protocol	EFF_F1	Line Plot of HAQ-DI	Unadjusted Mean ± SE	SAC
9.10	Per Protocol	EFF_F1	Line Plot of Analysis of Change from Baseline in HAQ-DI	Posterior Mean ± SD	SAC
9.11	Per Protocol	EFF_F1	Line Plot of SHAQ VAS Scales	Unadjusted Mean ± SE. Page by scale. Add footnote: "Note: US English version of SHAQ-VAS Questionnaire presented in the output."	SAC
9.12	Per Protocol	EFF_F1	Line Plot of Change from Baseline in SHAQ VAS Scales		SAC

Exploratory Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PhGA and PtGA					
9.13	Per Protocol	EFF_F1	Line Plot of Physician Assessment of Global Disease Activity	Unadjusted Mean ± SE.	SAC
9.14	Per Protocol	EFF_F1	Line Plot of Change from Baseline in Physician Assessment of Global Disease Activity	Unadjusted Mean ± SE.	SAC
9.15	Per Protocol	EFF_F1	Line Plot of Patient Assessment of Global Disease Activity	Unadjusted Mean ± SE.	SAC
9.16	Per Protocol	EFF_F1	Line Plot of Change from Baseline in Patient Assessment of Global Disease Activity	Unadjusted Mean ± SE.	SAC
CRISS					
9.17	Per Protocol	EFF_F2	Box Plots of CRISS	Panel by Visit (Day 85 and 197)	SAC
Home FVC					
9.18	Per Protocol	EFF_F3	Line plot of Weekly Home FVC (L)	No error bars	SAC
9.19	Per Protocol	EFF_F3	Line plot of Change from Baseline in Weekly Home FVC (L)	No error bars	SAC
9.20	Per Protocol	BIO_F4	Individual Subject Profiles for Weekly Home FVC (L) by Treatment Group		SAC
Correlation Analysis					
9.21	Per Protocol	EFF_F4	Correlation of Change in FVC vs Biomarker Endpoints	Panel by treatment group and grouped by individual subjects	SAC
9.22	Per Protocol	EFF_F4	Correlation of Change in mRSS vs Biomarker Endpoints		SAC
9.23	Per Protocol	EFF_F4	Correlation of Baseline OSM (Skin) vs Biomarker Endpoints and Change in mRSS		SAC
Notes: 1: Individual figure(s) will be produced for interim but may not be shared. Justification: DRCs follow the principle of presenting summary data where possible to reduce the degree of unblinding, so this output will only be presented if necessary.					

16.12.20. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.	Screened	ES7	Listing of Reasons for Screen failures		SAC
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	Enrolled	BL1	Listing of Subjects for whom the Treatment Blind was Broken		SAC
4.	Enrolled	TA1	Listing of Planned and Actual Treatments	Add footnote: Subject 600 was randomised in error to an incorrect strata before the day of dosing. This was reversed and they were correctly randomised on the day of dosing.	SAC
5.	Enrolled	SD2	Listing of Reasons for Study Treatment Discontinuation		Adhoc DRC, SAC
Protocol Deviations					
6.	Enrolled	DV2	Listing of Important Protocol Deviations		SAC
7.	Enrolled	IE3	Listing of Subjects with Inclusion/ Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	Enrolled	SP3	Listing of Subjects Excluded from Any Population	Do not show treatment group at interims, output by treatment group at final.	IA1, IA2, SAC
Demography					
9.	Enrolled	DM2	Listing of Demographic Characteristics	Do not show treatment group at interims, output by treatment group at final.	IA2, SAC
10.	Enrolled	DM9	Listing of Race		IA2, SAC
Concomitant Medications and Medical Conditions and Smoking History					

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
11.	Enrolled	CM3	Listing of Concomitant Medications	Do not show treatment group at interims, output by treatment group at final.	DEC, IA1, IA2, SAC
12.	Enrolled	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text		IA2, SAC
Exposure					
13.	Enrolled	EX3	Listing of Exposure Data	See 201246/final/ Listing 2 for the way that EX3 has been adapted. Order by treatment, subject then list doses in chronological order. Add summary variable stacked under participant details: 'Cumulative number of injections.' Note: This data would only be presented on request for interim analyses	DEC[1], IA1[1], IA2[1], SAC
14.	Enrolled	TBC	Listing of Reason for not Receiving Full Planned Dose	Listing of verbatim text collected when full dose not given as planned at a study visit attended by the participant.	Adhoc DRC, SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
15.	Enrolled	AE8	Listing of All Adverse Events	Do not show treatment group at interims, output by treatment group at final. Do use System Organ Class (as in AE8CP)	IA1, IA2, SAC
16.	Enrolled	AE8	Listing of Adverse Events of Severe Intensity	Do use System Organ Class (as in AE8CP) Show frequency.	SAC
17.	Enrolled	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
18.	Enrolled	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant AEs					
19.	Enrolled	AE8CP	Listing of Fatal Serious Adverse Events		SAC
20.	Enrolled	AE8CP	Listing of Non-Fatal Serious Adverse Events		SAC
21.	Enrolled	AE8CP	Listing of Serious Adverse Events		SAC
22.	Enrolled	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
23.	Enrolled	AECP8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Do not show treatment group at interims, output by treatment group at final.	Adhoc DRC, SAC
All Laboratory					
24.	Enrolled	LB5	Listing of Haematology Laboratory Values of CTCAE grade	Order by subject, then lab test Do not show treatment group at interims, output by treatment group at final.	IA1, IA2, SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
25.	Enrolled	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance	Order by subject, then category (e.g. Chemistry), then lab test Do not show treatment group at interims, output by treatment group at final.	IA1, IA2, SAC
26.	Enrolled	LB14	Listing of Laboratory Data with Character Results		SAC
Haematology					
27.	Enrolled	201246/Final/ listing 23	Listing of All Haematology Values and Changes from Baseline	See listing 23 in 201246. Report: Standard result Change from baseline and Percent change from baseline. Do not flag CTCAE grades Do not show treatment group at interims, output by treatment group at final.	IA1, IA2, SAC
Hepatobiliary (Liver)					
28.	Enrolled	LIVER5	Listing of Liver Events		SAC (may be reported at interim, conditional on data)

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Urinalysis					
29.	Enrolled	UR2	Listing of Urinalysis Results		SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ECG					
30.	Enrolled	EG3	Listing of All ECG Data for Subjects with Any Value of Potential Clinical Importance	Do not show treatment group at interims, output by treatment group at final.	IA1, IA2, SAC
31.	Enrolled	EG5	Listing of Abnormal ECG Findings		IA1, IA2, SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Vital Signs					
32.	Enrolled	VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance		SAC
Immunogenicity					
33.	Enrolled	IMM2	Listing of Immunogenicity Results		SAC
Other					
34.	Enrolled	201246/Final/ listing 23	Listing of Absolute and Changes from Baseline in Weight	As listing 26 for haematology, show standard result, change from baseline and % change from baseline	SAC
Notes: Listing will be produced for interim but may not be shared. Justification: DRCs follow the principle of presenting summary data where possible to reduce the degree of unblinding, so this listing will only be presented if necessary.					

16.12.21. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population (Disease Characteristics)					
35.	Enrolled	POP_L2	Listing of Systemic Sclerosis Disease Activity at Screening and Day 1	This requires deriving disease duration and combining results from more than one dataset. Do not show treatment group at interims, output by treatment group at final.	IA2, SAC
36.	Enrolled	POP_L1	Listing of Systemic Sclerosis Medication History	Do not show treatment group at interims, output by treatment group at final.	IA2, SAC
37.	Enrolled	POP_L3	Listing of Systemic Sclerosis Disease History		IA2, SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
38.	Enrolled	POP_L4	Listing of HRCT		SAC
39.	Enrolled	POP_L5	Listing of Historical and Baseline Autoantibody	Do not show treatment group at interims, output by treatment group at final.	IA2, SAC
40.	Enrolled	POP_L6	Listing of mRSS at Skin Biopsy Site		SAC
Pharmacokinetic					
41.	Enrolled	Based on PKCL1, see output for DEC	Listing of GSK2330811 Plasma Concentration-Time Data	Add data dependent footnote: 'Note: NA=Not Available [data dependent], NQ=Non-Quantifiable, LLQ value=100ng/mL'	DEC[1], IA1
42.	Enrolled	PKPL1	Listing of Derived GSK2330811 Pharmacokinetic Parameters per Participant	CPMS to produce this. Footnote: Parameters for individual participants are derived from PopPK analysis (empirical Bayes estimates).	IA1
43.	Enrolled	Based on PKCL1, see output for DEC	Listing of GSK2330811 Blister Serum Concentration-Time Data	Add data dependent footnote: 'Note: NA=Not Available [data dependent], NQ=Non-Quantifiable, LLQ value=100ng/mL'	IA2, SAC
Pharmacodynamic					
44.	Enrolled	Based on PKCL1, see output for DEC	Listing of Serum Level of OSM	By, Parameter (Include both Free and Total OSM) then treatment Add footnote: 'Note: BLQ = Below the limit of quantification which is 1.45 pg/ml for both free and total OSM.'	DEC[1], IA1, IA2
45.	Enrolled	Based on PKCL1, see output for DEC	Listing of Blister Serum Level of OSM	By, Parameter (Include both Free and Total OSM) then treatment Add footnote:	IA2, SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
				'Note: BLQ = Below the limit of quantification which is 1.45 pg/ml for both free and total OSM.'	
46.	PK	PKPL1	Listing of Derived Total OSM Parameters per Participant	CPMS to produce this. Footnote: Parameters for individual participants are derived from PopPK/PD analysis (empirical Bayes estimates).	IA1
Biomarkers					
47.	Enrolled	BIO_L1	Listing of Baseline Levels of Biomarkers	Baseline values only Don't present treatment group. By subject then ordered by endpoint type (Inflammation, Fibrosis, Vascular)	IA2
Patient Profile					
48.	Enrolled	ARR1	Listing of Arrhythmias	Refer IDSL Standard mock shell under Cardiovascular Events	SAC
Patient Profile					
49.	Enrolled	DV2	Listing of Subjects with COVID-19 Protocol Deviations	Do not include 'exclusion form analyses population' columns.	SAC
50.	Enrolled	PAN12	Listing of COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events		SAC
51.	Enrolled	PAN7	Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic	Add footnote: 'Note: COVID impact forms only collected for missed visits/ assessments from Day 113 onwards.'	SAC

Notes:

1: Listing will be produced for interim but **may** not be shared. Justification: DRCs follow the principle of presenting summary data for restricted data types where possible to reduce the degree of unblinding, so this listing will only be presented if necessary.

16.13. Appendix 13: List of Gene Modules

16.13.1. Disease Gene Modules

SSc vs HC Downregulated genes	SSc vs HC Upregulated genes				
MATN4	CPXM1	MX2	PAPPA	ARPC1B	GPX1
TNNI2	ASPN	OAS1	SLC16A3	IGSF6	COTL1
HMGCS1	SELE	ISG15	PLAC8	BASP1	HCLS1
INSIG1	LTF	IFIT3	CCR7	RAB31	ITGB2
SLC27A2	TNFSF4	IFI6	LTB	BGN	CTSC
LDHD	HP	MX1	VCAM1	TGFB3	AIF1
SLC14A1	LAMP5	IFI44	SCG2	SRPX	GMFG
SCGB3A1	SULF1	IFI27	SCRG1	COL6A3	MMP9
BTC	NOX4	CFB	BMX	COL15A1	CPXM2
SLC12A2	STMN2	GBP1	FZD2	A2M	SELP
SOX9	COMP	IDO1	CCR2	SLC1A3	MS4A7
PRSS12	ADAMTS4	PARP9	TDO2	ALDH1A3	SLCO2B1
SEMA3E	LUM	EPSTI1	TNFRSF12A	DYSF	MS4A4A
ZNF273	CTHRC1	RTP4	DOK5	CCR1	CD163
NPY1R	CGREF1	PLA1A	CEMIP	CYBB	C1QC
RNF128	C1QTNF6	STAT1	TNC	LY96	CCL13
PON3	COL5A2	KERA	SERPINE2	BATF3	CLEC4G
FAXDC2	COL8A1	LRRC15	CD93	LGI2	LRRC25
BCAT2	COL11A1	PRND	GEM	CTSZ	C1QB
GSN	SAA1	COL4A4	PXDN	STARD8	TNFSF13B
PCOLCE2	THBS4	CCL2	COL4A1	TLR1	PLEK
IGFBP6	IGKC	P4HA3	COL4A2	LGALS9	LILRB2
SP5	IGHM	NNMT	NID2	FCN1	CCR5
TSPAN8	POU2AF1	PRSS23	ALPK2	LILRB3	SLAMF8
ABCA6	AKR1B10	CTGF	CDH11	NUP62	CXCL10
GLRB	PTX3	INHBA	CHN1	RELB	CXCL11
PDGFRL	DKK1	THY1	THBS1	THEMIS2	CCL8
SGCG	NEFL	C1QTNF5	MMP11	IL3RA	SRD5A2
AGTR1	FPR1	PENK	RGS16	PLXDC1	FDCSP
ANGPTL5	C4A	C7	SYNDIG1	RNASE6	ADAMDEC1
SERPINA5	GDF15	CCL5	DIO2	LY86	CYR61
OSR2	IL6	IL2RA	GPR183	FKBP11	CCL3
PLPP3	SERPINE1	NKG7	GPR65	CD14	GZMB
WISP2	ADAM12	C1QTNF3	SPON1	CYBA	GZMA
ELANE	COL1A2	TNFAIP6	SULF2	ALOX5AP	UBD
ASIP	ELN	TIMP1	WISP1	C2	CCL4
KAZALD1	ACTA1	CH25H	RAB3C	DAB2	GBP5
GSTM5	WFDC1	FMO3	PDPN	CD68	RGS1
F10	IFI44L	IGF1	IGFBP7	IFITM2	TIMD4
IGFBP5	RSAD2	PCSK5	ANGPT2	IFITM3	CXCL9
WIF1	OAS2	NR2F1	STC2	SLC15A3	SFRP4
FGFBP2	BST2	IGFBP4	RBP5	IFITM1	

16.13.2. Lung Fibrosis Gene Module

COL6A3	IGHM
UBD	C6
PLA2G2A	LTF
MMP1	CPXM1
SPP1	ADAM12
SFRP4	COL5A1
SULF1	GEM
POSTN	TGFB3
CXCL13	CFI
IGF1	COL5A2
TDO2	PDE1A
ASPN	SERPINE2
THY1	TNC
COL15A1	VCAM1
FNDC1	LAMP5
COL10A1	CPXM2
CTHRC1	THBS4
SAA1	LGI2
IGFBP4	P4HA3
SULF2	DIO2
FAM92B	MMP11

16.13.3. Cell-type specific gene modules

cell module signatrues from Tocilizumab paper (Lancet 2016)		
GSEA: M2-Macrophage Gene Set	GSEA: M1-Macrophage Gene Set	GSEA: Fibrosis Gene Set
CCL13	CCL19	COMP
TNFSF13	CXCL9	COL10A1
TNFSF10	CCL5	COL4A1
PYGL	CCL14	POSTN
SDC1	IL32	COL15A1
FN1	CXCL11	COL1A2
GATM	CXCL10	COL1A1
HRH1	EBI3	COL12A1
PDGFC	CCL15	COL18A1
TGFBR2	CHI3L2	COL5A2
COTL1	GBP1	COL5A1
MS4A4A	PLA1A	CTHRC1
MS4A6A	IDO1	COL14A1
EVI2B	CD38	COL16A1
CD209	GBP2	COL3A1
CLEC10A	PDE4B	COL7A1
CTNNAL1	CCR7	DIO2
SEPP1	IFI27	LOXL1
MBP	SLAMF7	LOXL2
CD9	IFIT3	NOX4
FGL2	UBD	FN1
NRP1	LAMP3	IGF1
MSR1	TSPAN13	CTGF
CD14	TNFAIP6	THY1
CD36	ADAM19	ACTA2
CD302	C1S	MXRA5
CD163	IFITM1	CDH11
MRC1	IL7R	GREM1
CLEC7A	CD40	SERPINE1
CLEC4A	IL2RA	THBS2
EVI2A	FAS	ITGA11
	IL15RA	ADAM12
		FAP
		GLI1
		GLI2
		SFRP2
		IGFBP7

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