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

Title	:	Reporting and Analysis Plan for 201789: A Phase 1/2, Double-Blind, Placebo-Controlled Study of the Pharmacokinetics, Safety and Tolerability of GSK3196165 in Combination with Methotrexate Therapy, in Japanese Subjects with Active Moderate-Severe Rheumatoid Arthritis Despite Treatment with Methotrexate.
Compound Number	:	GSK3196165
Effective Date	:	24-JAN-2018

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201789.
- This RAP is intended to describe the pharmacokinetic, safety, immunogenicity, efficacy, pharmacodynamic and pharmacokinetic/pharmacodynamic analyses required for the study.
- This version includes amendments to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This RAP describes all planned analyses and outputs required for the final Clinical Study Report (CSR) of study 201789.
Protocol	• This RAP is based on the protocol [(Dated: 27/SEP/2016) of study 201789 (GSK Document No. : 2016N278580_01] and eCRF.
Primary Objective	• To assess the pharmacokinetics of GSK3196165 in Japanese rheumatoid arthritis (RA) subjects • To assess the safety and tolerability of GSK3196165 in combination with methotrexate (MTX) therapy in Japanese RA subjects.
Primary Endpoint	• Pharmacokinetic (PK) parameters of GSK3196165 calculated from sparse sampling concentrations. • Incidence of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest.
Study Design	• This is a randomized, double-blind, parallel group, 3 dosage level, placebo-controlled, Phase 1/2 study in Japanese subjects with active moderate-severe RA despite treatment with MTX.
Planned Analyses	• Final analyses will be performed according to the steps described in Section 3.1. • All decisions regarding final analyses, as defined in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.
Analysis Populations	• The Intent to Treat (ITT) population consists of all subjects who were randomized to treatment and receive at least one dose of study treatment. This population will be used for the efficacy and safety analyses. • PK population consists of all GSK3196165-treated subjects from whom PK samples are collected and analyzed.
Hypothesis	• No formal hypotheses will be tested.
Primary Analyses(PK)	• For serum concentration of GSK3196165 over time, individual data will be listed and presented in graphical form, and summary statistics at each time point will be calculated by each dose level. The following PK variables after the last dosing will be derived by non-compartmental analysis as applicable and as data allowed: Cmax, tmax, AUCtau, AUC(0-t), AUC(0-inf), and t1/2. For PK parameters, summary statistics will be calculated by each dose level, and scatter plots against the dose level will be generated. Dose proportionality will also be assessed with the power model.
Primary analyses(Safety and Tolerability)	• All AEs will be coded using MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of subjects with any AEs will be summarized by dose. The study treatment-related AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be reported separately.

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan_Study201789_Final [23-MAY-2017]	
Reporting and Analysis Plan_Study201789_final_Amend 1 [04-OCT-2017]	
Section 3.1 and Section 3.2	Removed these sections because the planned interim analyses have been canceled.
Section 3.3	Removed this section and added the unblinding process.
Section 3.1	Removed "(interim and final)".
Section 8.2.1	Added the listing of change from baseline in DAS28(CRP)
Section 9.1	Added the listings of ACR response, Categorical DAS28 response and DAS28 remission
Section 9.1	Added the listing of change from baseline in DAS28(ESR)
Section 11.4.3	Removed the Reporting area for interim analyses
Section 11.4.3	Amended the area for final reporting
Section 11.10.1	Amended the Numbering according to the change of the TLF.
Section 11.10.2	Removed the delivery description for interim analyses
Section 11.10.3, Section 11.10.4, Section 11.10.5, Section 11.10.6 and Section 11.10.12	Removed the TOC of TLF for interim analyses.
Section 11.10.9 and Section 11.10.10	Amended the TOC to simplify it.
Section 11.10.11	Amended the typos.
Section 11.10.12	Added the listings of ACR20/50/70, Categorical DAS28 response and DAS28 remission
Reporting and Analysis Plan_Study201789_final_Amend 2 [24-Jan-2018]	
Section 4.	Removed "valid" to avoid misunderstanding.
Section 6.1.3.	Added the description of RF and ACPA analyses.
Section 7.1.3.2.	Added one pharmacokinetic parameter "AUC(0-t)" for dose proportionality.
Section 7.2.1.	Added 3 AESI listings (Infection, Hypersensitivity Reactions and Injection Site Reaction)
Section 8.1.1.	Removed the summary of change from baseline in Borg scale becase this variable is categorical.
Section 8.1.3.	Added the details of Immunogenicity analyses because of clarification of data in detail
Section 11.2.	Clarified that early withdrawal visits will be included for Assessment Windows.
Section 11.5.2	Added the reference date for Age calculation
Section 11.5.2	Added the definitions of Age Group and Age Category
Section 11.5.2	Amended the procedure for average daily dose of OCS to calculate it at only each scheduled visit.
Section 11.5.3	Amended the specification of AESI because the procedure to specify AESI was changed.
Section 11.5.4	Clarified that when calculating ACR, Patient's Assessment for Arthritis Pain "at this time" will be used.
Section 11.5.4	Amended the typos in SJC and TJC section.
Section 11.10.	Amended Shell IDs and titles. Added some displays.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

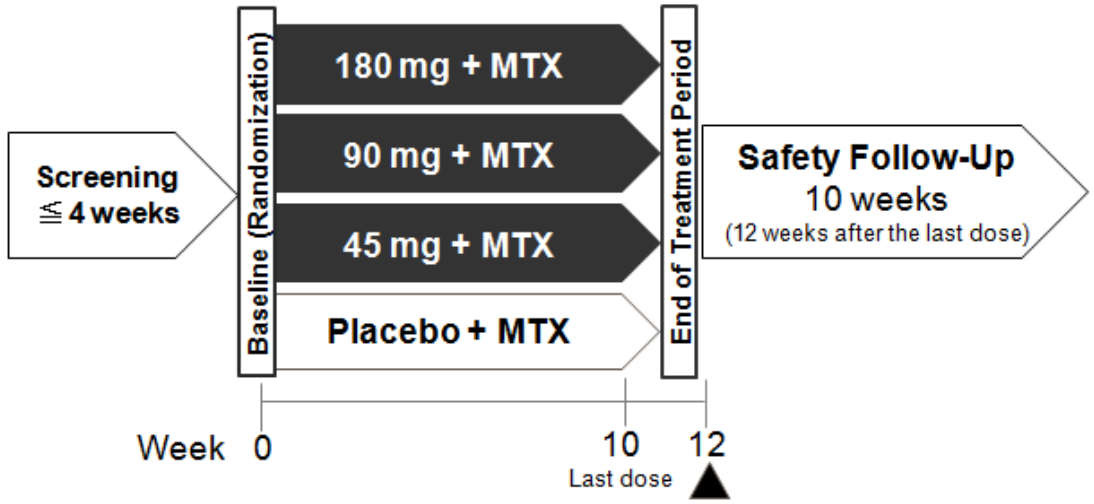
There were no changes or deviations to the originally planned statistical analysis specified in the protocol [(Dated: 27/SEP/2016)].

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the PK of GSK3196165 in Japanese RA subjects	• PK parameters of GSK3196165 calculated from sparse sampling concentrations
• To assess the safety and tolerability of GSK 3196165 in combination with MTX therapy in Japanese RA subjects	• Incidence of AEs, SAEs and AEs of special interest
Secondary Objectives	**Secondary Endpoints**
• To assess the safety other than primary endpoints • To assess the efficacy in Japanese RA subjects	• Vital signs, 12-lead ECG and laboratory assessment • Immunogenicity (anti-GSK3196165 antibody) • Change from baseline in Disease Activity Score 28 [DAS28(CRP)] at all assessment timepoints
Exploratory	
Efficacy Endpoints	
At all efficacy assessment timepoints • ACR 20/50/70 response rate • Change from baseline in DAS28(ESR) • Proportion of subjects achieving categorical DAS28(CRP) / DAS28(ESR) response (moderate/good EULAR response) • Proportion of subjects achieving DAS28(CRP) / DAS28(ESR) remission. • Change from baseline in Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) • Change from baseline in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue • Note: For composite endpoints, e.g., DAS28(CRP), ACR Response, etc., each component of the assessment will also be reported. Results over time, reflecting all assessment time points, will also be reported.	
Biomarker Endpoints	
• Pharmacodynamic biomarkers to assess target engagement (e.g., serum concentration of free GM-CSF, GM-CSF-GSK3196165 complex) • Pharmacodynamic biomarkers which may be predictive of response to GSK3196165 (e.g., 14-3-3η, MRP8/15, ARGS neoepitope, YKL-40) • Pharmacodynamic biomarkers to assess response to GSK3196165 (e.g. IL-6, IL-1β, TNFα, IL-17A, IL-17F) • Whole blood ribonucleic acid (RNA) analysis	
Safety Biomarkers	
• Biomarkers which may be indicative of lung damage (e.g. SP-D, KL-6, cholestenoic acid) • Baseline concentrations of GM-CSF autoantibodies	

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a randomized, double-blind, parallel group, 3 dosage level, placebo-controlled, Phase 1/2 study in Japanese RA subjects.
Dosing	• This study is composed of up to 4 weeks screening period, 12 weeks treatment period (last dose Week 10), and 10 weeks follow-up period (12 weeks from last dose). • Treatment with GSK3196165 or placebo will be given weekly as a single subcutaneous (SC) injection by an unblinded administrator. There will be 5 weekly injections (Day 1, 8, 15, 22, 29), then every other week (EOW) injections at Day 43, 57 and 71.
Treatment Assignment	• Subjects will be randomized (1:1:1:1) to placebo or one of three SC GSK3196165 doses at Day 1 (Week 0).
Interim Analysis	• No interim analysis in midstream of the treatment period is planned. • Once all subjects have completed visits in the treatment period, an interim analysis may be performed to discuss within GSK and consult with the regulatory authority on the future development plan of GSK3196165.

2.4. Statistical Hypotheses

The primary objective of this study is to assess the PK, safety and tolerability of GSK3196165 in combination with MTX therapy in Japanese RA subjects. No formal hypotheses to be tested. Two-sided 90% confidence interval (CI) will be used for PK estimation.

3. PLANNED ANALYSES

3.1. Final Analyses

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

1. All subjects 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 prodcedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screening	• Comprise of all subjects who are given subject number and of whom data are collected at screening.	• Study Population
Randomised	• All subjects who are randomized to treatment. • Any subject who receives a treatment randomization number will be considered to have been randomized.	• Study Population
ITT	• All subjects who are randomized to treatment and who receive at least one dose of study treatment.	• Study Population • Efficacy • Safety
PK	• This population consists of all GSK3196165-treated subjects from whom PK samples are collected and analyzed.	• PK
Immunogenicity	• The immunogenicity population will consist of all subjects in the ITT population, who had at least one immunogenicity assessment.	• Immunogenicity

NOTES :

- Please refer to Appendix 10: List of Data Displays which details the population to be used for each displays being generated.

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 summarised and listed.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Time & Events
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Treatment States and Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Multiple Comparisons & Multiplicity
11.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the All Screening, Randomised and ITT population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition for the Subject Conclusion Record	Y		
Reasons for Subject Withdrawal			Y
Treatment Status and Reasons for Discontinuation of Study Treatment	Y		Y
Screening Status and Reasons for Screen Failure	Y		Y
Subjects Who Were Rescreened			Y
Subjects Enrolled by Site ID	Y		
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Populations Analysed			
Study Populations	Y		
Exclusions from ITT Population	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Baseline Efficacy Parameters	Y		
RF and ACPA	Y		Y
Age Ranges	Y		
Race and Racial Combinations	Y		Y [1]
RA Disease History	Y		Y
Substance Use	Y		Y
Prior and Concomitant Medications			
Medical Conditions			Y
Medications	Y		Y
Medications for RA prior to the Date of first dose	Y		
Medications for RA from the Date of first dose	Y		
Relationship of Medication Class, Dictionary Term and Verbatim Text			Y
Oral Corticosteroid by Visit	Y		
Change from Baseline in Oral Corticosteroid by Visit	Y		
Non-drug therapy			Y
Exposure and Treatment Compliance			
Exposure to Study Treatment	Y		Y
Exposure to MTX	Y		Y

NOTES :

- Y = Yes display generated.

[1] Listing of race.

6.1.1. Demographic Characteristics

The following items will be summarized and listed by dose group in addition to those as standard.

- BMI
- Family history for Cardiovascular risk factor

6.1.2. Baseline Efficacy Parameters

The following efficacy parameters at baseline will be summarized by dose group.

- DAS28(CRP, ESR)
- CRP, ESR
- Swollen Joint Count 66
- Tender Joint Count 68
- SDAI, CDAI
- Patient's Global Assessment of Arthritis
- Physician's Global Assessment of Arthritis
- Patient's Assessment of Arthritis Pain (current and past week's pain)
- HAQ-DI score
- FACIT-Fatigue

6.1.3. Rheumatoid Factor and Anti-cyclic Citrullinated Protein Antibody

The number and percentage of RF positives and ACPA positives will be summarized.

6.1.4. RA disease history

RA disease history will be summarized in form of disease duration categorical (< 2 years/ ≥2 years) and as summary statistics (in month), RA functional class and time since start of RA symptoms. Disease duration and time since start of RA symptoms are defined in the Appendix 5.

6.1.5. Corticosteroid use

Value and change from baseline in average daily prednisolone dose will be summarized and listed by visit. Average daily dose is defined in the Appendix 5.

6.1.6. Exposure

The extent of exposure to GSK3196165 and MTX will be evaluated by summarizing and listing the following items, respectively. These items are defined in the Appendix 5.

6.1.6.1. GSK3196165

- The number of injections
- Cumulative dose in mg
- The duration of drug exposure in days

6.1.6.2. MTX

- Overall average weekly dose

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacokinetic Analyses

7.1.1. Overview of Planned Pharmacokinetic Analyses

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

Table 3 provides an overview of the planned analyses, with full details being presented in Appendix 10: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Endpoint / Parameter/ Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Serum GSK3196165 Concentrations														
Serum Concentration				Y	Y	Y	Y							
PK Parameters														
Parameters				Y			Y				Y			
Dose Proportionality								Y				Y		

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.1.2. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Process & Standards).

7.1.3. Pharmacokinetic Parameters

7.1.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Process & Standards).
- The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin (version 6.3 or higher).
- All calculations of non-compartmental parameters will be based on actual sampling times.
- PK parameters described in Table 4 will be determined from the serum GSK3196165 concentration-time data, as data permits.

Table 4 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUCtau	Area under the concentration-time curve from time zero (pre-dose in Visit 10) to 336 hr post-dose (Visit 12). If a sampling time deviation occurred at nominal time 336 hours after administration (and 336 < t), AUCtau will be calculated using the concentration at time 336 hours after administration post-dose estimated by the method of interpolation. If nominal time 336 hours after administration > t (or if the concentration at time 336 hours after administration was below then limit of quantification), then the concentration (y) at time 336 hours after administration is estimated using λz and last observed Ct according to the formula: $y=Ct(obser) \times e^{-\lambda z(336-t)}$ Then the following equation will be used to calculate (AUCtau=AUC(0-336) after last-dosing) where t is the time of last quantifiable serum concentration. AUCtau = AUC(0-t) + AUC(t-336) If λz is not estimable, a AUC(t-336)is not calculated (when 336 > t). (NOTE: λz is the apparent terminal phase rate constant.)
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose in Visit 10) to the time of the last quantifiable concentration (C(t)) will be calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (i.e., Linear Up/Log Down calculation method in Phoenix WinNonlin Professional). NOTE: Ct is the last observed quantifiable concentration.
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose in Visit 10) extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
%AUCex	The percentage of AUC(0-inf) obtained by extrapolation (%AUCex) will be calculated as: **[AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100**

Parameter	Parameter Description
Cmax	Maximum observed concentration after last dosing (Visit 10), determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
tlast	The time of the last measurable (positive) concentration.
t1/2	Apparent terminal half-life will be calculated as: **t1/2 = ln2 / lambda_z**
lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the curve.
lambda_z_lower	The lower limit on time for values to be included in the calculation of Lambda z.
lambda_z_upper	The upper limit on time for values to be included in the calculation of Lambda z.
#pts	The number of time points used in computing Lambda z.
R2	The goodness of fit statistic for the terminal elimination phase.

NOTES:

- Additional parameters may be included as required.

7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

The following PK statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined serum profiles).

Pharmacokinetic Statistical Analyses
Drug Concentration Measurements
• Summary statistics, by dose group and nominal time point, will be calculated for the concentration of GSK3196165 in serum. • Individual serum concentration-time profiles will be plotted. Also median/mean profiles will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the $\log_e$-transformed scale (i.e. semi-log plot). • Mean/Median profiles by dose group will be plotted. Each of figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. a log-linear plot). • Individual subject serum concentrations of GSK3196165 will be listed by dose group and nominal time. The items to be listed are center, subject, age, sex, race, dose, date, planned relative time, actual time, time deviation, actual relative time and concentration by dose groups.
Deriving and Summarizing Pharmacokinetic Parameters
• The summary tables will be produced for the derived serum GSK3196165 PK parameter. Summary statistics will be calculated for each parameter by dose groups. • All the derived PK parameters for GSK3196165 will be listed, by subject and dose group. The items to be listed are center, subject, age, sex, race, dose, Cmax, Tmax, AUCtau, AUC(0-t), AUC(0-inf), %AUCex and t1/2. • Individual parameter, tlast, lamda_z, lamda_z_lower, lamda_z_upper, #pts and R2 will be listed. Summary statistics will not be calculated. • The steady-state will be examined graphically by plotting the Ctrough of Visit 2 - Visit 12 [Visit2 (Day 1), Visit4 (Day 8), Visit5 (Day 15), Visit7 (Day 29), Visit9 (Day 57), Visit10 (Day 71), Visit12 (Day 85)].

Pharmacokinetic Statistical Analyses
Dose proportionality
• Dose proportionality of GSK3196165 for Cmax, AUCtau, AUC(0-t) and AUC(0-inf) will be evaluated using the power model defined as follows. $\log(Y_i) = \mu + \beta * \log(D_k) + \varepsilon_i$ Y_i The measured response variable of PK parameter(Cmax, AUCtau, AUC(0-t) and AUC(0-inf)) for *i*th subject μ Intercept β Slope of loge-transformed dose D_k Dose (k=1: 45mg, 2: 90mg, 3: 180mg) ε_i Random error following normal distribution $N(0, \sigma^2)$ • The power model will be fitted to loge-transformed PK parameters data using SAS Proc Mixed with loge-transformed dose as fixed effect. An estimate of the slope with corresponding 90% CI will be estimated from the power model to assess the degree of dose-proportionality (slope β around unity indicates dose-proportionality). Point estimates for the slopes of PK parameters with associated 90% CI will be presented. • If data permit, mean profile of Cmax, AUCtau, AUC(0-t) and AUC(0-inf) will be plotted. Each of the figures will contain one plot on linear and logarithmic scales.

7.2. Safety Analyses

The safety analyses will be based on the ITT population, unless otherwise specified. The summaries will be presented based on the AEs during on-treatment period. The listings will be presented based on the AEs during entire study. On-treatment is defined in the Appendix 3.

7.2.1. Overview of Planned Adverse Event Analyses

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 5 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC and PT	Y		Y
All AEs by SOC and PT and Maximum Intensity	Y		
AESI	Y		
AESI – Serious Infections and Non Serious Pulmonary or Opportunistic Infections			Y
AESI – Systemic Hypersensitivity Reactions			Y
AESI – Injection Site Reaction			Y
Adverse Events by Overall Frequency	Y		
Drug-Related AEs by SOC and PT	Y		
Drug-Related AEs by SOC and PT and Maximum Intensity	Y		
Common Non-Serious Adverse Events by SOC and PT	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT and Verbatim Text			Y
AEs Leading to Withdrawal from Study	Y		
AEs Leading to Permanent Discontinuation of Study Treatment	Y		
AESI Leading to Permanent Discontinuation of Study Treatment	Y		
Disease Related Events	Y		Y
Serious AEs			
Serious AEs			Y
Serious AEs by SOC and PT	Y		

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8. SECONDARY STATISTICAL ANALYSES

8.1. Safety Analyses

8.1.1. Overview of Planned Other Safety Analyses

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

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 6 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y					
Change from Baseline in ECG Values by Visit				Y		
ECG values by Visit	Y		Y			
Abnormal ECG Findings			Y			
Vital Signs						
Change From Baseline in Vital Signs by Visit				Y		
Vital Signs by Visit	Y		Y			
Pulmonary						
Cough by Visit and Grade	Y		Y			
Lung Auscultation by Visit	Y		Y			
Pulse Oximetry by Visit	Y		Y	Y		
Borg Dyspnea Scale by Visit	Y		Y			
FEV_1 by Visit	Y		Y	Y		
FVC by Visit	Y		Y	Y		
D_{LCO} by Visit	Y		Y	Y		
Respiratory events						
Persistent cough with grade 2 or greater recorded	Y		Y			
Persistent dyspnea with grade 3 or greater recorded	Y		Y			
Persistent D_{LCO} by >15%	Y		Y			
Hepatic B Virus						
HBV DNA monitoring			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated,
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.1.1.1. Pulmonary assessment

All pulmonary assessment results (Cough, Lung Auscultation, Pulse Oximetry, Borg Dyspnea Scale, FEV_1, FVC and D_{LCO}) will be listed.

The values and the changes from baseline for the FEV_1, FVC, D_{LCO} and Pulse Oximetry will be summarized. The number and percentages of subjects having a cough for each grade and each Borg dyspnea scale will be summarized by visit.

8.1.1.2. Respiratory events

Numbers and percentages of subjects experiencing persistent cough, or persistent dyspnea or persistent D_{LCO} decrease will be reported in a table by dose group at the start time of the event.

The definitions of these events are described in the Appendix 5.

8.1.2. Overview of Planned Clinical Laboratory Analyses

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

If a subject fails any of the laboratory inclusion/exclusion criteria, laboratory test related to the inclusion/exclusion criteria may be repeated in screening period. The data collected by retests are not at screening visit but unscheduled visit. Therefore the summary at Screening visit will not be presented and baseline values defined in the Appendix 4 will be summarized.

Table 7 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Changes from Baseline				Y		
Chemistry by visit	Y		Y			
Emergent Chemistry Results Relative to Normal Range	Y					
Hematology						
Hematology Changes From Baseline				Y		
Hematology by Visit	Y		Y			
Emergent Hematology Results Relative to Normal Range	Y					
Urinalysis						
Urinalysis Dipstick Results	Y		Y			
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting			Y[1]			
Hepatobiliary Laboratory Abnormalities	Y[1]					
Medical Conditions for Subjects with Liver Stopping Events			Y[1]			
Substance Use for Subjects with Liver Stopping Events			Y[1]			
Liver Monitoring/Stopping Event Reporting			Y[1]			
Liver Stopping Event Information for RUCAM Score			Y[1]			
Liver Biopsy Details			Y[1]			
Liver Imaging Details			Y[1]			

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Laboratory Tests (Antigen and Antibody) for Liver Events			Y[1]			
Laboratory Tests (DNA and RNA) for Liver Events			Y[1]			
Cardiovascular						
ECG Findings in Cardiovascular Events			Y[2]			
Subjects who had Cardiovascular Events			Y[2]			
Diagnostic Test for Cardiovascular Events			Y[2]			
Findings about Cardiovascular Events			Y[2]			
Healthcare Resource Utilization due to Cardiovascular Events			Y[2]			
NYHA Functional Class for Cardiovascular Events			Y[2]			
Death in Cardiovascular Events			Y[2]			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- RUCAM: Roussel Uclaf Causality Assessment Method
- [1]: if at least one Liver event occurs, this display will be presented.
- [2]: if at least one Cardiovascular event occurs, this display will be presented.

8.1.3. Immunogenicity Analyses

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

The positive subjects of Anti-GSK3196165 Binding Antibody Detection are defined as those of which tests at Confirming are “positive”, and otherwise negative. The positive subjects of Neutralising Antibody detection are defined those of which tests at Screening are “positive”, and otherwise negative.

The number and percentage of positive and negative subjects will be summarized. Shift table from baseline to every assessment will be produced to assess the number of subjects going from:

- negative→negative
- negative→positive
- positive→negative
- positive→positive

Anti-GSK3196165 Binding Antibody Detection (posistive/negative) will be listed together with titre value (mL) and Rheumatoid Factor (positive/negative) for each subject with at least one positive result of Anti-GSK3196165 Binding Antibody Detection.

Table 8 Overview of Immunogenicity Analyses

[Endpoint / Parameter/ Display Type]	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Immunogenicity				Y			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2. Efficacy Analyses

8.2.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the ITT population, unless otherwise specified.

Table 9 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 9 Overview of Planned Efficacy Analyses

[Endpoint / Parameter/ Display Type]	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
DAS28 (CRP)														
Values				Y			Y				Y	Y		Y
Longitudinal data analysis								Y	Y					
Dose response analysis at Week 12								Y	Y					

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.2. DAS28 (CRP)

DAS28(CRP) values will be listed and summarized by dose group and nominal time. Mean and Median change from baseline versus time profile by dose group will be plotted.

8.2.2.1. Planned Efficacy Statistical Analyses

Statistical Analyses –Mixed Model with Repeated Measures–
Endpoint(s)
• Change from baseline in DAS28 (CRP)
Model Specification

• This endpoint will be analyzed using a mixed-models repeated measures (MMRM) approach.
• Analysis will include the following fixed effects:
  • Dose group as a categorical variable
  • Visit as a categorical variable
  • Baseline DAS28(CRP) as a continuous variable
  • Dose-by-visit interaction
  • Visit-by-baseline interaction
• An unstructured variance structure will be used to model the within-patient errors.
• Analyses will be done with the MIXED Procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• LSmeans for each dose will be presented along with the associated 95% CI. • Point estimates and their associated 95% CI will be calculated for the differences between each GSK3196165 dose group and Placebo (GSK3196165 – Placebo). • The primary treatment comparison will be the contrast between the GSK3196165 groups to placebo.

Statistical Analyses – Dose response Analysis –
Endpoint(s)
• Change from baseline in DAS28 (CRP) at Week 12.
Model Specification

• The following non-linear models will be fitted exploratory.
 	
$$DAS28(CRP)_i = E_0 + \frac{E_{\max} Dose_i}{Dose_i + ED_{50}} + \varepsilon_i$$
 	
$$DAS28(CRP)_i = E_0 + \frac{E_{\max} Dose_i^B}{Dose_i^B + ED_{50}^B} + \varepsilon_i$$
 	
$$DAS28(CRP)_i = E_0 + E_1 \times Dose_i + \varepsilon_i$$
 	
• The notation in the formula is as below:
  • Subscript i denotes i-th subject.
  • E_0 : Response at dose 0 (placebo)
  • E_{max} : Maximum effect (for reduction, Emax≤0; for increase, Emax≥ 0)
  • ED_{50} : Dose at which 50% of maximum effect is reached

Statistical Analyses – Dose response Analysis –

- B : a slope factor
- E_1 : Coefficient of a linear model.
- ε_i : Residual error following $N(0,\sigma^2)$

- The dose will be set to zero for all placebo data.
- Starting values for the iterations will be chosen based on the observed data as appropriate. For example;
  - E_0 : Mean in Placebo
  - E_{max} : Mean difference between 180 mg and Placebo (180 mg – Placebo)
  - ED_{50} : 90 (= (180 – 0) / 2)
  - B = 1
- Each of the models will be fitted to the data and their fit compared using the Akaike information criteria (AIC).
- The model with the smallest AIC will be selected as the final model for inference.

Model Checking & Diagnostics

- Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

Calculation procedure for the 95% CIs using a bootstrap method

- The 95% CIs will be calculated in accordance with the following procedure.
  1. Recreate the dataset by sampling with replacement from the original dataset by dose group.
     - Use a PROC SURVEYSELECT with SEED = 161216 to generate the bootstrap dataset
  2. Fit the final dose response model to the dataset in step 1. Estimate the parameters of interest $\hat{\theta}_1$ and compute $g(\hat{\theta}_1)$ {g is any arbitrary function.}
  3. Repeat steps 1-2, for b = 1, 2, ..., B (B=10,000) to obtain $\hat{\theta}_1, \hat{\theta}_2, \ldots, \hat{\theta}_B$ and compute $g(\hat{\theta}_1), g(\hat{\theta}_2), \ldots, g(\hat{\theta}_B)$.
  4. Select 2.5% quantile of the $\hat{\theta}_b$ and $g(\hat{\theta}_b)$ as the lower limit and 97.5% quantile as the upper limit.

Model Results Presentation

- The result of the final model will be presented.
- The estimates of model parameters and their 95% CI will be presented.
- From the fitted model, predictive responses for each of the doses will be calculated along with 95% CI.
- The differences between each GSK3196165 dose and Placebo and their 95% CI will be calculated from the fitted model.
- A plot of the residuals versus predicted values will be examined to assess distuributional assumptions.
- The results of the other models will be shown as only SAS outputs.

9. EXPLORATORY STATISTICAL ANALYSES

9.1. Overview of Planned Exploratory Analyses

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

Table 10 provides an overview of the planned exploratory analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 10 Overview of Planned Exploratory Analyses

[Endpoint / Parameter/ Display Type]	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Efficacy Endpoints														
ACR 20/50/70 response														
Proportion at each assessment				Y	Y		Y							
DAS28(ESR)														
Values				Y			Y				Y	Y		Y
Longitudinal data analysis								Y	Y					
SDAI, CDAI and FACIT-Fatigue														
Values				Y			Y				Y	Y		
Longitudinal data analysis								Y	Y					
Categorical DAS28(CRP) / DAS28(ESR) response DAS28(CRP) / DAS28(ESR) remission														
Proportion at each assessment				Y			Y							
Other endpoints														
Swollen (28, 66) & Tender (28, 68) Joint Count				Y			Y				Y			
Patient's Assessment of Arthritis Pain (current pain/past week's pain)				Y			Y				Y			
Patient's Global Assessment of Arthritis				Y			Y				Y			
Physician's Global Assessment of Arthritis				Y			Y				Y			
CRP, ESR				Y			Y				Y	Y		
HAQ-DI score				Y			Y				Y	Y		

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated, HAQ-DI: Health Assessment Questionnaire Disability Index
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

9.1.1. ACR 20/50/70 response

The number and percentage of responder will be presented. The difference of response rate from Placebo and the associated 95% CI will be calculated. The 95% CI will be based on normal approximation.

The percentage of ACR 20/50/70 responder by dose group will be plotted, respectively.

9.1.2. DAS28 (ESR)

DAS28(ESR) values will be listed and summarized by dose group and nominal time. Mean and median change from baseline versus time profiles by dose group will be plotted.

Statistical Analyses –Mixed Model with Repeated Measures–
Endpoint(s)
• Change from baseline in DAS28(ESR)
Model Specification

• This endpoint will be analyzed using a MMRM approach.
• Analysis will include the following fixed effects:
  • Dose group as a categorical variable
  • Visit as a categorical variable
  • Baseline DAS28(ESR) as a continuous variable
  • Dose-by-visit interaction.
  • Visit-by-baseline interaction.
• An unstructured variance structure will be used to model the within-patient errors.
• Analyses will be done with the MIXED Procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Point estimates and their associated 95% CI will be calculated for the differences between each GSK3196165 dose group and Placebo (GSK3196165 – Placebo). • The primary treatment comparison will be the contrast between treatments at week 12.

9.1.3. SDAI, CDAI and FACIT-Fatigue

SDAI, CDAI and FACIT-Fatigue scores will be listed and summarized by dose group and nominal time. Mean and median change from baseline versus time profiles by dose group will be plotted.

Statistical Analyses –Mixed Model with Repeated Measures–
Endpoint(s)
• Change from baseline in SDAI, CDAI and FACIT-Fatigue
Model Specification
• This endpoint will be analyzed using a MMRM approach.

Statistical Analyses –Mixed Model with Repeated Measures–

• Analysis will include the following fixed effects:
  • Dose group as a categorical variable
  • Visit as a categorical variable
  • Baseline as a continuous variable
  • Dose-by-visit interaction
  • Visit-by-baseline interaction
• An unstructured variance structure will be used to model the within-patient errors.
• Analyses will be done with the MIXED Procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• LSmeans for each dose will be presented along with the associated 95% CI. • Point estimates and their associated 95% CI will be calculated for the differences between each GSK3196165 dose group and Placebo (GSK3196165 – Placebo).

9.1.4. Categorical DAS28 Response

A good or moderate response will be combined to form the "responder" category. The number and percentage of responders will be presented. The difference of response rate from Placebo and the associated 95% CI will be calculated. The 95% CI will be based on normal approximation.

9.1.5. DAS28 Remission

The number and percentage of remission from Placebo will be presented. The difference of remission rate and the associated 95% CI will be calculated. The 95% CI will be based on normal approximation.

9.1.6. Other endpoints

The other endpoints as below will be listed and summarized by dose group and nominal time as well as changes from baseline. Changes from baseline in only CRP, ESR and HAQ-DI will be plotted by dose group, respectively.

- Swollen Joint Count (28 and 66)
- Tender Joint Count (28 and 68)
- Patient's Assessment of Arthritis Pain
  - Current pain
  - Past week's pain
- Patient's Global Assessment of Disease Activity
- Physician's Global Assessment of Arthritis

- CRP (in mg/L), ESR (in mm/hr)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)

9.2. Pharmacodynamic and Biomarker Analyses

9.2.1. Overview of Planned Pharmacodynamic and Biomarker Analyses

The pharmacodynamic analyses will be based on the ITT population, unless otherwise specified.

Table 11 provides an overview of the planned pharmacodynamic and Biomarker analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 11 Overview of Planned Pharmacodynamic and Biomarker Analyses

Endpoint / Parameter/ Display Type	Untransformed													
	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
free soluble GM-CSF and soluble GM-CSF complexed to GSK3196165														
Values				Y	Y		Y				Y	Y		Y
MRP8/14, ARGS neoepitope, YKL-40 and 14-3-3η.														
Values				Y	Y		Y				Y	Y		Y
IL-6, IL-1β, TNFα, IL-17A and IL-17F														
Values				Y	Y		Y				Y	Y		Y
SP-D, KL-6 and cholestenoic acid														
Values				Y	Y		Y				Y	Y		Y
measurement of GM-CSF autoantibodies at baseline														
Values				Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Biomarkers/pharmacodynamic endpoint values will be listed and summarized by dose group and nominal time. Mean and median versus time profiles by dose group will be plotted.

9.3. Pharmacokinetic / Pharmacodynamic Analyses

A graphical PK/PD exploration will be conducted to complement the statistical dose-response analysis and to visualize the nature of the concentration-response correlation. A variety of graphs will be generated per subject and in overall, where GSK3196165 concentration is characterised by the individual values, and the response is characterised by the individual values of the pharmacodynamic markers or efficacy.

Pharmacokinetic and pharmacodynamic data from this study may be combined with historical data (e.g. BAROQUE) for the purpose of further exploratory analysis (including population pharmacokinetic and/or PK/PD modelling as appropriate) which may be reported separately from the main clinical study report.

- Linear scatterplot of change from baseline in PD values (free soluble GM-CSF, GM-CSF-GSK3196165 complex) at each visit versus GSK3196165 concentration values at corresponding visit
- Linear scatterplot of change from baseline in CRP levels at each visit versus GSK3196165 concentration values at corresponding visit
- Linear scatterplot of change from baseline in DAS28(CRP) measures at each visit versus GSK3196165 concentration values at corresponding visit

10. REFERENCES

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11. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.1	Appendix 1: Time and Events
Section 11.2	Appendix 2: Assessment Windows
Section 11.3	Appendix 3: Treatment States & Phases
Section 11.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Immunogenicity
Section 11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.7	Appendix 7: Multiple Comparisons and Multiplicity
Section 11.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 11.9	Appendix 9: Abbreviations & Trade Marks
Section 11.10	Appendix 10: List of Data Displays

11.1. Appendix 1: Time & Events

11.1.1. Protocol Defined Time & Events

Procedures	Screen-ing	Baseline		Treatment Period									FU		Last Visit	EW[1]
	Visit															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	Week															
	(up to 4 weeks)	0		1	2	3	4	6	8	10		12	15	18	22	
	Day															
		1	3*	8	15	22	29	43	57	71	74*	85	106	127	155	
Allowance			±1 day					±3 days			±1 day	±3 days	±1 week			
Written Informed Consent(s)	X															
Subject Demography	X															
Medical, Disease, Therapy History	X															
Inclusion/Exclusion Criteria	X															
Efficacy and PRO Assessments[3]																
Swollen (66) & Tender (68) Joint Count[2]	X	X[4]		X	X		X	X	X			X			X	X
Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis[3]	X	X[4]		X	X		X	X	X			X			X	X
HAQ-DI[3]	X	X[4]		X	X		X	X	X			X			X	X
FACIT-Fatigue[3]		X[4]					X					X			X	X

Procedures	Screen-ing	Baseline		Treatment Period									FU		Last Visit	EW[1]
	Visit															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	Week															
	(up to 4 weeks)	0		1	2	3	4	6	8	10		12	15	18	22	
	Day															
		1	3*	8	15	22	29	43	57	71	74*	85	106	127	155	
Allowance			±1 day					±3 days			±1 day	±3 days	±1 week			
Safety Evaluations[5]																
Concomitant Medication	X	X	Record all concomitant medications													
Height[6], Body weight	X						X					X			X	X
Other Physical Examination[7]	X	X[4]		X	X		X		X			X			X	X
Vital Signs	X	X		X	X	X	X	X	X	X		X			X	X
12-lead ECG[8]	X											X				X
AEs/SAEs/AESIs	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cough, Lung Auscultation, Pulse Oximetry, Borg Dyspnea Scale	X	X[4]		X	X	X	X	X	X	X		X			X	X
Chest X-ray[10]	X															
Spirometry (FEV_1, FVC)	X											X			X	X
D_{LCO}	X[11]											X			X	X
Laboratory Assessments																
Hematology, Chemistry (except for lipid and pregnancy test)	X	X[4]			X		X		X			X			X	X

Procedures	Screen-ing	Baseline		Treatment Period									FU		Last Visit	EW[1]
	Visit															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	Week															
	(up to 4 weeks)	0		1	2	3	4	6	8	10		12	15	18	22	
	Day															
		1	3*	8	15	22	29	43	57	71	74*	85	106	127	155	
Allowance			±1 day					±3 days			±1 day	±3 days	±1 week			
Urinalysis (dip stick)	X						X		X			X			X	X
Cholesterol, triglycerides, HDL, LDL[12]		X[4]										X			X	X
Pregnancy test[13]	S	U					U		U			U			U	U
TB, HBsAg, HepB cAb, HBs Ab, HepC Ab, HIV, HBV DNA**	X															
HBV DNA monitoring (HBs Ab positive subject only)							X		X			X	X	X	X	X
RF, ACPA (anti-CCP)	X															
ESR[14]		X[4]		X	X		X	X	X			X			X	X
CRP	X	X[4]		X	X		X	X	X			X			X	X
Other Laboratory Assessments																
PK blood sampling (GSK3196165)[15]		X[4]	X	X	X		X		X	X	X	X	X	X	X	X
Free GM-CSF, GM-CSF-GSK3196165 complex		X[4]	X	X	X		X		X	X		X			X	X
PD blood biomarkers		X[4]			X		X					X				X
RNA blood biomarker		X[4]										X			X	X

Procedures	Screen-ing	Baseline		Treatment Period								FU		Last Visit	EW[1]
	Visit														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	Week															
	(up to 4 weeks)	0		1	2	3	4	6	8	10		12	15	18	22	
	Day															
		1	3*	8	15	22	29	43	57	71	74*	85	106	127	155	
Allowance			±1 day					±3 days			±1 day	±3 days	±1 week			
PGx sampling DNA[16]		X[4]														
Lung biomarkers		X[4]										X			X	X
Immunogenicity (anti-GSK3196165 antibody)[17]		X[4]			X		X					X			X	X
Anti-GM-CSF auto-antibodies		X[4]														
Study Treatment GSK3196165/placebo[18]		X		X	X	X	X	X	X	X						

ACPA: Anti-cyclic citrullinated protein antibody, CCP: Cyclic citrullinated peptide, ESR: Erythrocyte sedimentation rate, FVC: Forced vital capacity, HBV: Hepatitis B virus, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, RF: Rheumatoid factor.

1. All subjects who withdraw from the study should have an early withdrawal (EW) visit as soon as possible after study agent discontinuation and then return for a follow-up visit (the last visit) for 10 weeks
   (12 weeks after last dose of study medication).
2. The same individual (where possible) should perform all disease assessments for an individual subject.
3. PRO assessments should be conducted before any tests, procedures, assessments or consultations, to avoid influencing the subjects' perception.
4. Assessments may be performed up to 24hours before dosing GSK3196165/placebo.
5. All safety evaluations should be conducted before dosing GSK3196165/placebo.
6. Height will be measured at only screening.
7. Complete physical at screening, and then limited physical examination (see Section 7.4.7 in the Protocol) thereafter.

8. ECG should be performed before vital signs, blood draws, and dosing (triplicate ECGs required at screening, and single thereafter unless there are safety concerns, in which case repeats may be required
(see Section 7.4.9 in the Protocol).
9. Only SAEs related to study participation or related to a GSK product will be recorded from the time a subject consents to participate in the study.
10. Unless performed within previous 12 weeks (No need to repeat if subject re-screened).
11. Chest HRCT if D_{LCO} ≥60% - <70% predicted (No need to repeat if subject re-screened).
12. ≥8 hours fasting required before blood draw.
13. For women of child-bearing potential. S=serum; U=urine.
14. ESR measured locally.
15. PK sampling should be collected before dosing at the visits scheduled study treatment (GSK3196165/placebo). At the visits doesn't scheduled study treatments, it may be collected in any time during the
visit. (Day 3, 74, 85, 106, 127, 155, and early withdrawal visit).
16. In consenting subjects.
17. In addition to these scheduled immunogenicity assessments, “event-driven” testing will also be employed for those subjects that experience anaphylaxis, serious hypersensitivity, or AEs related
to study drug administration that led to withdrawal from the study (see Section 7.5 in the Protocol).
18. GSK3196165 or placebo must be administered on the same day each week ±1 day for the first 5 weekly doses, thereafter on the same day EOW ±3 days for bi-weekly doses.
* The Day 3 (Visit 3) blood sample must be drawn 2 days (±1 day is allowable) after the first dose, and the Day 74 (Visit 11) blood sample must be drawn 3 days (±1 day is allowable) after the last dose.
** HBV-DNA sample will be collected from all subjects, and HBV-DNA will be tested for only subjects with HBs Ab positive.

11.2. Appendix 2: Assessment Windows

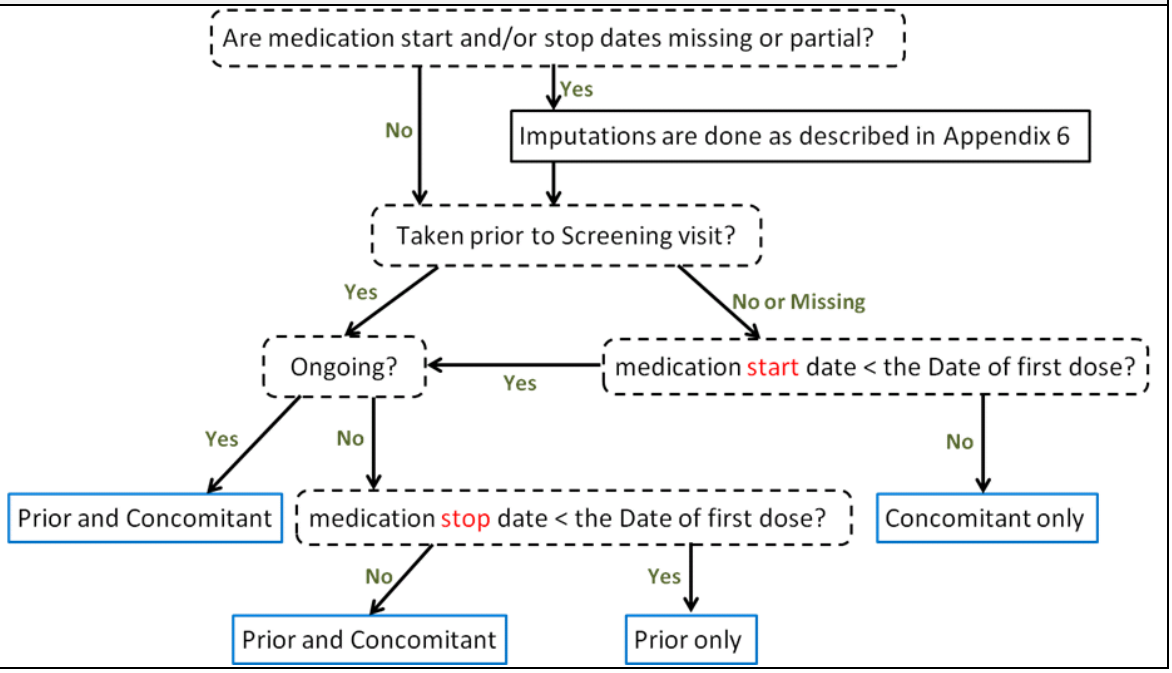
Data at the scheduled visit defined by Appendix 1 will be summarized according to this RAP. Data out of the allowances will not be slotted to a particular time point, but will be listed as unscheduled and early withdrawal unless otherwise specified.

In case that the one allowance contains more than two assessments, the first assessment will be treated as the scheduled and the others as the unscheduled.

11.3. Appendix 3: Treatment States and Phases

11.3.1.1. Treatment States for Concomitant Medications for Rheumatoid Arthritis (CONMEDS RA) Data

Treatment State	Definition
Prior only	CONMEDs RA Stop Date < the Date of first dose of study medication
Prior and Concomitant	CONMEDs RA Start Date < the Date of first dose of study medication CONMEDs RA Stop Date ≥ the Date of first dose of study medication
Concomitant only	CONMEDs RA Start Date ≥ the Date of first dose of study medication
Flowchart	



11.3.1.2. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-treatment	Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 12 weeks
Post-treatment	AE Start Date > Study Treatment Stop Date + 12 weeks
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date, = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date, = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Onset Time Since last Dose (Days)	If Treatment Stop Date > AE Onset Date, = AE Onset Date - Treatment Stop Date If Treatment Stop Date ≤ AE Onset Date, = AE Onset Date - Treatment Stop Date + 1 Missing otherwise
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship to GSK3196165/Placebo is marked 'YES' on Inform/CRF OR value is missing.
MTX-related	If relationship to Methotrexate is marked 'YES' on Inform/CRF OR value is missing.

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo	Placebo	1
B	GSK3196165 45 mg	GSK3196165 45 mg	2
C	GSK3196165 90 mg	GSK3196165 90 mg	3
D	GSK3196165 180 mg	GSK3196165 180 mg	4

NOTES:

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

11.4.2. Baseline Definition & Derivations

11.4.2.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the latest pre-dose assessment.

11.4.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.4.2.1 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 change from baseline displays.

11.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: arenv\arprod\gsk3196165\mid201789\final_02
QC Spreadsheet	:arenv\arprod\gsk3196165\mid201789\final_02\qc

Reporting Process
Analysis Datasets
• Analysis datasets will be created according to Legacy GSK A&R dataset standards OR CDISC standards (SDTM IG Version 3.1.3 & AdaM IG Version 1.0. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will not be generated.

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the randomized group the subject 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.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables, except for the Respiratory events and the laboratory items which may be re-tested. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.

Reporting Standards	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
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)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	Tmax
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits 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 randomization date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

11.5.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Age will be calculated based on date of Screening visit as an Age reference date for Screen failed subjects and based on date of the initial dose date for ITT population.
Age Group

• The following category will be used for Summary of Demography.
  ○ Age ≤ 18 (years)
  ○ 19 < Age < 64
  ○ 65 ≤ Age

Age Category

• The following category will be used for Summary of Age Ranges.
  ○ Age < 18 (years)
  ○ 18 ≤ Age ≤ 64
  ○ 65 ≤ Age ≤ 84
  ○ 85 ≤ Age

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

Demographics

RA disease history

RA Disease Duration

- RA disease duration will be calculated based on the formula:

  Disease Duration in Months = [Treatment Start Date – (RA Diagnosis Date)] / 30.25 rounded to four decimals

  Disease Duration in Years = [Treatment Start Date – (RA Diagnosis Date)] / 365.25 rounded to four decimals

Time since start of RA symptoms

- Time since start of RA symptoms will be calculated based on the formula:

  Time since start of RA symptoms in Months = [Treatment Start Date – (Date of first symptom)] / 30.25 rounded to four decimals

Prior and Concomitant Medications

Oral Corticosteroid

- To assess corticosteroid use and determine average daily corticosteroid dose, all corticosteroid dosages will be converted to a prednisolone equivalent in milligrams by multiplying the dose of the steroid (using the coded term from GSKDrug) by the conversion factor to get prednisolone equivalent units.
- The following table will provide the conversion factors.
- For each scheduled visit, the average daily prednisolone dose will be calculated by summing all prednisolone doses since the previous visit up to and including the current visit and then dividing by the number of days in this period (**Date of current visit – Date of previous scheduled visit**).
- If frequency that a subject takes the steroid is less than once daily such as QOD, the dosage will be converted to daily dose and then the average daily dose will be calculated. For example, if a subject takes 10 mg of the steroid QOD, the daily dose is 5 mg/day.

Conversion	Steroid
8.333	BETAMETHASONE
0.2	CORTISONE
6.667	DEXAMETHASONE
0.25	HYDROCORTISONE
1.25	METHYLPREDNISOLONE
1	PREDNISOLONE
1.25	TRIAMCINOLONE

Rheumatoid factor (RF)

- A subject who has a value of RF > 15 IU/mL is positive.
- Otherwise negative.

Anti-cyclic Citrullinated Protein Antibody (ACPA)

- A subject who has a value of ACPA $\geq$ 4.5 U/mL is positive.
- Otherwise negative.

Extent of Exposure

GSK3196165

- Number of days of exposure to study drug will be calculated based on the formula:

  Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1
- Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.
- The cumulative dose will be based on the formula:

  Cumulative Dose = Sum of (Actual Volume x One Dosage / Expected Volume)
- The following table provides the one dosage and the expected volume in each dose group.

Dose group	One Dosage (mg)	Expected volume (mL)
Placebo	0	0.6
45 mg	45	0.3
90 mg	90	0.6
180 mg	180	1.2

Methotrexate (MTX)

- Overall Average Weekly MTX dose will be averaged across Week 1 - 12for each subject based on the formula:

  Overall Average Weekly MTX Dose = Mean of the Weekly Dosage of MTX

11.5.3. Safety

Adverse events of special interest will be derived using Common Terminology Criteria for Adverse Events, 2009 v4.0 (CTCAE).

Adverse Events of Special Interest

Adverse Events of Special Interest are defined as the AEs below. AESI will be specified by Safety Review Team and Japan EST.

- Serious infections, including serious respiratory infections and TB.
- Opportunistic infections
- Neutropenia
- Respiratory events as AESI
- Pulmonary alveolar proteinosis
- Hypersensitivity reactions, including anaphylaxis
- Injection site reactions

Respiratory events

Events	Definition
Persistent cough with Grade 2 or greater recorded	Cough grade 2 or greater recorded for 3 consecutive weeks (15 or more days) on the eCRF page.
Persistent dyspnea with Grade 3 or greater recorded	Borg Scale grade 3 or greater recorded for 3 consecutive weeks (15 or more days) on the eCRF page.

Respiratory events	
Events	**Definition**
Persistent decrease of D_{LCO} by > 15%	Relative decrease of D_{LCO} of >15% compared to baseline for 3 consectuvie weeks (15 or more days) **Decrease of D_{LCO} = (%change from baseline in D_{LCO}) $\times$ -1** A subject's baseline D_{LCO} value will be taken as the lowest value obtained from the Screening assessment or any unscheduled visit in between Screening and Day 1 visit.
Final adjudication will be conducted by the SRT.	

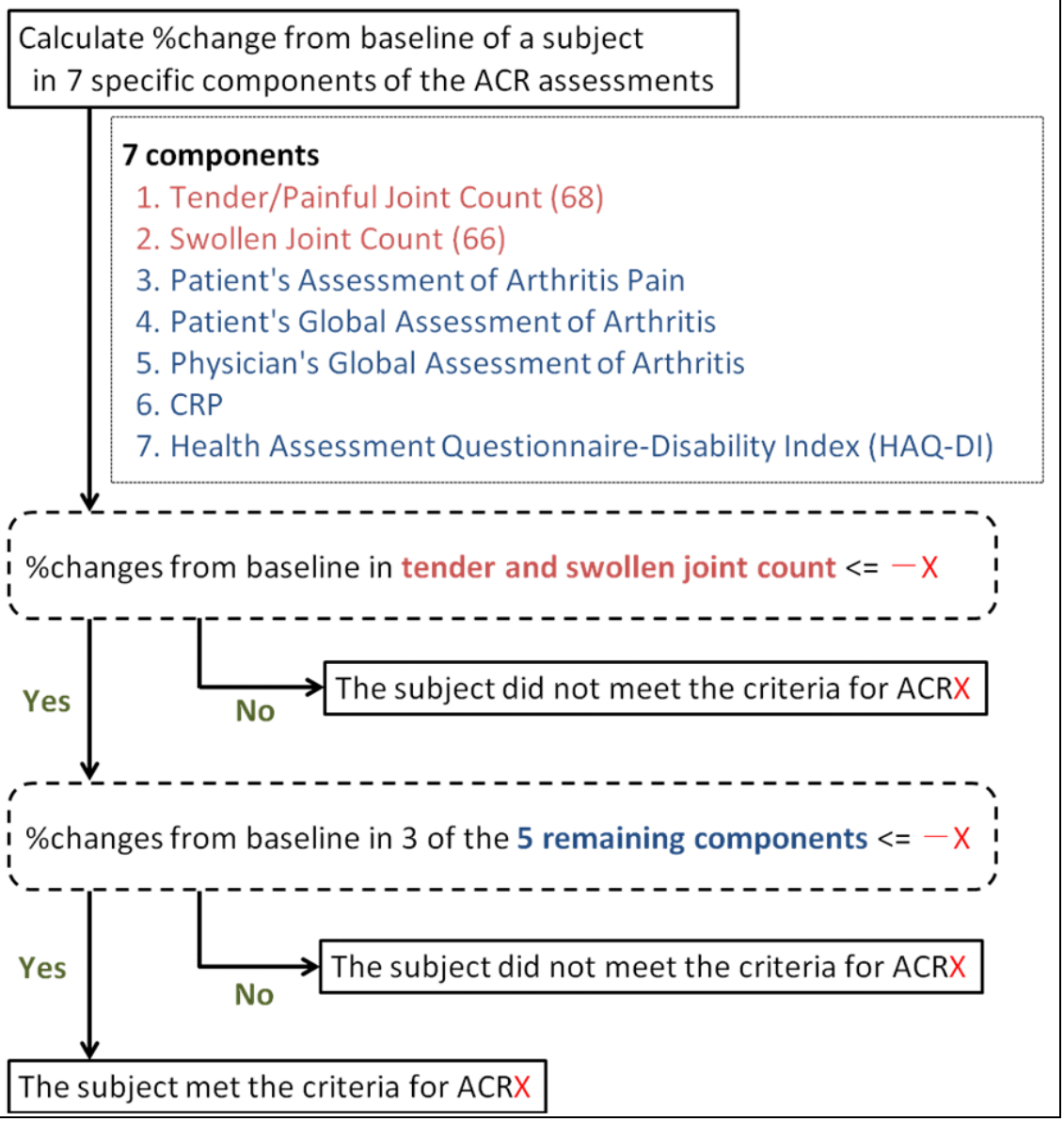
Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than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

11.5.4. Efficacy

ACR 20/50/70 response[American Collenge of Rheumatology Committee to Reevaluate Improvement Criteria, 2007]
Procedure

• The following 7 ACR-core set measures will define ACR20/50/70 response.
  • Tender/Painful Joint Count 68 (TJC68)
  • Swollen Joint Count 66 (SJC66)
  • Patient's Assessment of Arthritis Pain at this time
  • Patient's Global Assessment of Arthritis
  • Physician's Global Assessment of Arthritis
  • C-reactive protein (CRP) (in mg/L)
  • Health Assessment Questionnaire-Disability Index (HAQ-DI)
• The %Change from Baseline in each ACR-core set measure will be calculated.
• If %Change from Baseline in both tender and swollen joint counts are less than -20% and those in 3 of the 5 remaining ACR-core set measures are less than -20%, ARC20 criteria is met.
• Similarly ACR50 and 70 are calculated with the respective percent improvement.
• For all visits if any of the component scores are missing, then those scores will considered as not having met the criteria for improvement. Therefore, if TJC68 or SJC66 or 3 or more of the 5 remaining ACR-core set measures are missing, ACR20/ ACR50/ ACR70 will each be considered as "no response"
• For component scores with missing Baseline values or a Baseline value of 0, the percentage improvement cannot be calculated and the component will be considered as not having met the criteria for improvement for all visits.

Flowchart


Calculate %change from baseline of a subject in 7 specific components of the ACR assessments
7 components
1. Tender/Painful Joint Count (68)
2. Swollen Joint Count (66)
3. Patient's Assessment of Arthritis Pain
4. Patient's Global Assessment of Arthritis
5. Physician's Global Assessment of Arthritis
6. CRP
7. Health Assessment Questionnaire-Disability Index (HAQ-DI)
%changes from baseline in tender and swollen joint count <= −X
Yes
No
The subject did not meet the criteria for ACRX
%changes from baseline in 3 of the 5 remaining components <= −X
Yes
No
The subject did not meet the criteria for ACRX
The subject met the criteria for ACRX

Examples

- The subject did not met the criteria for ACR20

Component	Baseline	Post-dose visit value	%change
TJC68	43	14	-67
SJC66	38	44	16
Patient's Assessment of Arthritis Pain	46	20	-57
Patient's Global Assessment of Arthritis	85	31	-64
Physician's Global Assessment of Arthritis	75	27	-64
CRP	2.8	2.0	-29
HAQ-DI	11.6	7.2	-38

- The subject met the criteria for ACR50 but not ACR70

Component	Baseline	Post-dose visit value	%change
TJC68	43	14	-67
SJC66	38	14	-63
Patient's Assessment of Arthritis Pain	46	10	-78
Patient's Global Assessment of Arthritis	85	31	-64
Physician's Global Assessment of Arthritis	75	27	-64
CRP	2.8	1.0	-64
HAQ-DI	11.6	1.2	-90

Disease Activity Score[Prevoo**,** 1995**;** Fransen**,** 2005**;** Wells**,** 2009**]**

- The DAS assessment is a derived measurement with differential weighting given to each component. The DAS28 (CRP) and DAS28 (ESR) will be calculated at each assessment time point.
- The components of the DAS28 arthritis assessment include:
  - Tender Joint Count 28 (TJC28)
  - Swollen Joint Count 28 (SJC28)
  - C-reactive protein (CRP) (in mg/L) or Erythrocyte sedimentation rate (ESR) (in mm/hr)
  - Patient's Global Assessment of Arthritis (PtGA) (visual analogue scale with values from 0 = best to 100 = worst)

DAS28 (CRP)

- The DAS28 (CRP) will be calculated using the following formula:

$$DAS28(CRP) = 0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.36 \times \ln(CRP + 1) + 0.014 \times PtGA + 0.96$$

- If one of the components is missing at an individual assessment point, the DAS28 (CRP) value for that assessment will be set to missing

DAS28 (ESR)

- The DAS28 (ESR) will be calculated using the following formula:

$$DAS28(ESR) = 0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.70 \times \ln(ESR) + 0.014 \times PtGA$$

- If one of the components is missing at an individual assessment point, the DAS28 (ESR) value for that assessment will be set to missing. An ESR value of 0 will be substituted with ESR = 1 for the calculation of DAS28 (ESR).

Categorical DAS28 Response

- DAS28 (CRP) and DAS28 (ESR) will be categorized using EULAR response criteria. Response at a given time point is defined based on the combination of current DAS28 score andDAS28 decrease from baseline. The definition of no response, moderate response and good response is captured in the following table:
- DAS28 decrease from baseline value will be calculated using the following formula:

DAS28 decrease from baseline = DAS28 Baseline – Post-Dose Visit DAS28 Value

Current DAS28	DAS28 decrease from baseline		
	>1.2	>0.6 to ≤1.2	≤0.6
≤3.2	Good response	Moderate response	No response
>3.2 to ≤5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

- If the post-baseline DAS28 (CRP) or DAS28 (ESR) is missing, then the corresponding EULAR category will be missing.

DAS28 Remission

- DAS28 (CRP) remission is achieved by a DAS28 (CRP) value lower than 2.6.
- DAS28 (ESR) remission is achieved by a DAS28 (ESR) value lower than 2.6.
- Missing DAS28 values will be considered as not achieving remission.

Health Assessment Questionnaire-Disability Index (HAQ-DI)[Fries**,** 1980**;** Matsuda**,** 2003**]**

Procedure

- The functional status of the subject will be assessed by means of the Disability Index of the Health Assessment Questionnaire. This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas:
  - Dressing & grooming
  - Arising
  - Eating
  - Walking
  - Hygiene

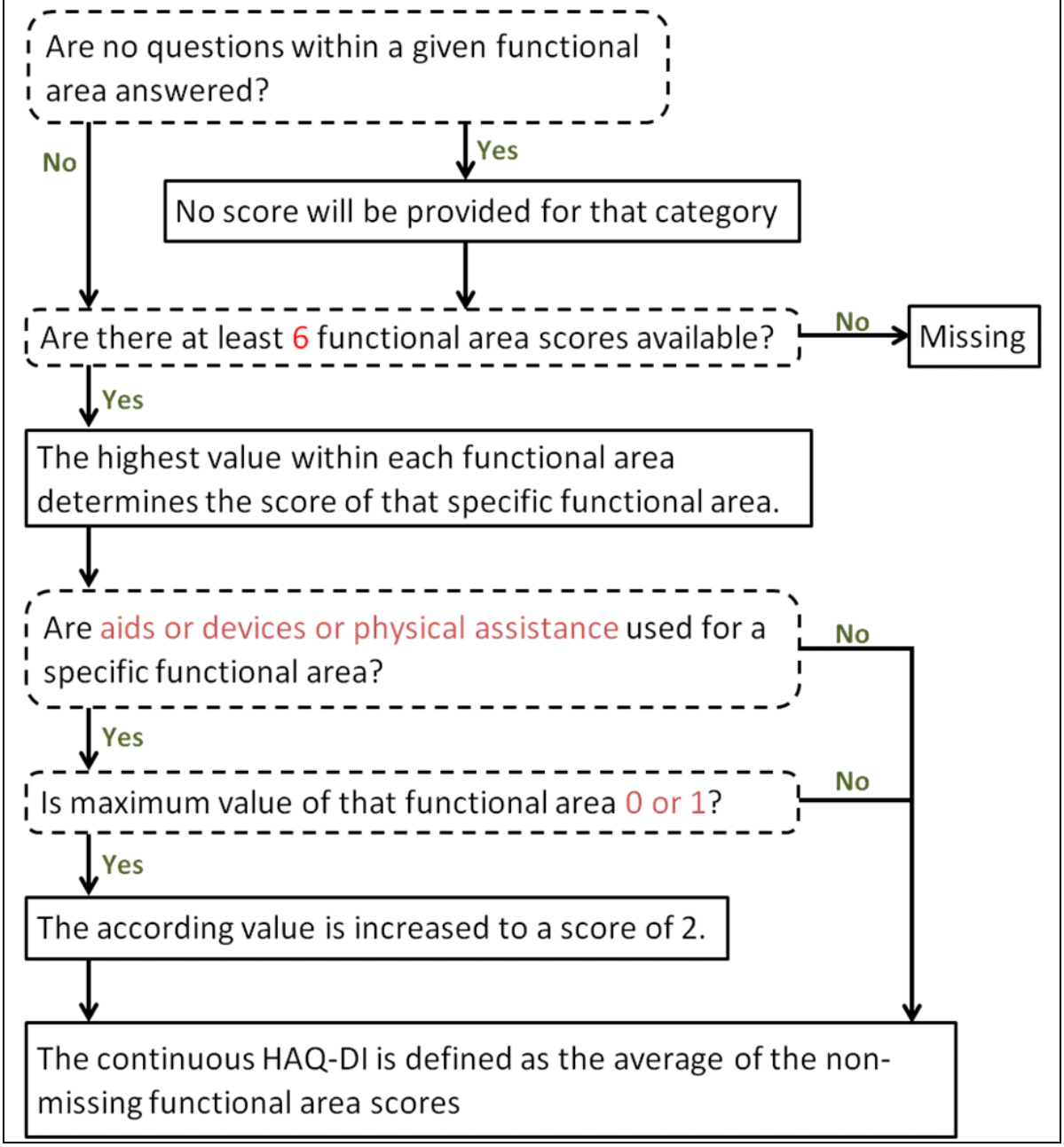
- Reach
- Grip
- Activities

- Each functional area contains at least two questions. For each question, there is a four level response set that is scored from 0 (without any difficulty) to 3 (unable to do). If aids or devices or physical assistance are used for a specific functional area and the maximum response of this functional area is 0 or 1, the according value is increased to a score of 2.

Aid or device	Functional area
Devices used for dressing	Dressing and grooming
Special or built up chair	Arising
Built up or special utensils	Eating
Cane	Walking
Crutches	Walking
Walker	Walking
Wheelchair	Walking
Bathtub seat	Hygiene
Bathtub bar	Hygiene
Raised toilet seat	Hygiene
Long-handled appliances in bathroom	Hygiene
Long-handled appliances for reach	Reach
Jar opener	Grip

- Regarding these corrections, the highest response within each functional area determines the score of that specific functional area. If no questions within a given functional area were answered, no score will be provided for that category (even if answers on aids or equipment are available).
- HAQ-DI is only calculated if there are at least 6 functional area scores available.
- The average of these non-missing functional area scores defines the continuous HAQ-DI score ranging from 0 to 3. If there are less than 6 functional area scores available, no imputation will be done and the HAQ-DI will be set to missing for the according assessment.

Flowchart


Are no questions within a given functional area answered?
Yes
No score will be provided for that category
No
Are there at least 6 functional area scores available?
No
Missing
Yes
The highest value within each functional area determines the score of that specific functional area.
Are aids or devices or physical assistance used for a specific functional area?
No
Yes
Is maximum value of that functional area 0 or 1?
No
Yes
The according value is increased to a score of 2.
The continuous HAQ-DI is defined as the average of the non-missing functional area scores

Examples

Value in each question

No.	Functional area	Value
1	Dressing and grooming	1
2	Dressing and grooming	0
3	Arising	2
4	Arising	1
5	Eating	3
6	Eating	0
7	Eating	2
8	Walking	1
9	Walking	0
10	Hygiene	2
11	Hygiene	2
12	Hygiene	1
13	Reach	0
14	Reach	0
15	Grip	3
16	Grip	2
17	Grip	0
18	Activities	2
19	Activities	1
20	Activities	0

Use of aid or device / Need for help

Functional area	Use or Need
Dressing and grooming	×
Arising	○
Eating	×
Walking	○
Hygiene	×
Reach	○
Grip	×
Activities	×

Maximum value in each functional area

Functional area	Score	Use of aid	Updated score
Dressing and grooming	1	×	1
Arising	2	○	2
Eating	3	×	3
Walking	1	○	2
Hygiene	2	×	2
Reach	0	○	2
Grip	3	×	3
Activities	2	×	2
		Sum updated scores	17
		Divide by number of functional area scored	2.125

This score was not updated because it was more than 2

This score was increased to 2 because it was 0 or 1.

FACIT-Fatigue

Procedure

- The FACIT-Fatigue questionnaire is a patient-reported measure developed to assess fatigue consisting 13 statements regarding feeling fatigue using a numeric rating scale ranging from 0 (Not at all) to 4 (very much).
- For only two of the items (i.e. An5 and An7) a higher value represents a lower fatigue, 11 of the item scores (i.e. HI7, HI12, An1, An2, An3, An4, An8, An12, An14, An15, An16) have to be reversed by subtracting the captured value from 4 (0 is turned to a 4, 1 into 3, 3 into 1, 4 into 0).
- After performing the reversals, the sum of the non-missing individual items will be multiplied by 13 and divided by the number of the non-missing individual items.
- The final score ranges from 0 to 52 with higher values representing a lower fatigue.
- If more than 6 individual items are missing at an assessment the FACIT-Fatigue score will be set to missing at that assessment.

Examples

Item Code	Reverse Item		Item Response		Item Score
HI7	4	—	2	=	2
HI12	4	—	4	=	0
An1	4	—	3	=	1
An2	4	—	1	=	3
An3	4	—	3	=	1
An4	4	—	0	=	4
An5	0	+	2	=	2
An7	0	+	1	=	1
An8	4	—	2	=	2
An12	4	—	3	=	1
An14	4	—	1	=	3
An15	4	—	2	=	2
An16	4	—	3	=	1
				Sum individual item scores	23
				Multiply by 13 =	299
				Divide by number of items answered =	23
				Fatigue Subscale Score =	**23**

SDAI[Smolen, 2003]

- The Simplified Disease Activity Index (SDAI) is a composite score consisting of the sum of SJC28, TJC28, PtGA/10, PhGA/10, and CRP **(mg/dl).**
- This score will be calculated based on the formula:

SDAI = SJC28 + TJC28 + PtGA / 10 + PhGA / 10 + CRP

- If one of the components is missing at an individual assessment point, the SDAI value for that assessment will be set to missing.

CDAI[Aletaha**,** 2005**]**

- The Clinical Disease Activity Index (CDAI) is a composite score consisting of the sum of SJC28, TJC28, PtGA/10, PhGA/10.
- This score will be calculated based on the formula:

CDAI = SJC28 + TJC28 + PtGA / 10 + PhGA / 10

- If one of the components is missing at an individual assessment point, the CDAI value for that assessment will be set to missing.

Swollen and Tender/Painful Joint Count

- Four different scores will be calculated to evaluate swelling and tenderness of joints.SJC28 and TJC28 will take 28 joints into account, SJC66 and TJC68 will use 66 and 68 joints, respectively.
- The assessment for swelling is the total number of joints with a present swelling and ranges from 0 to 28 for SJC28 and 0 to 66 for SJC66.
- The assessment for tenderness is the total number of joints with a present tenderness and ranges from 0 to 28 for TJC28 and 0 to 68 for TJC68.
- The following 28 joints will be taken into account for TJC28 and SJC28.
    - Shoulder (2 joints)
    - Knee (2)
    - Elbow (2)
    - Wrist (2)
    - Fingers (PIP, MCP: 20)
- Additionally the following joints will be taken into account for TJC68 and SJC66.
    - Temporomandibular (2)
    - Stemoclavicular (2)
    - Acromioclavicular (2)
    - Fingers (DIP: 8)
    - Ankle (2)
    - Tarsus (2)
    - Toes (PIP, MTP: 20)
    - Hip (2, only for TJC)
- If there are missing observations for tender or swollen joints then the remaining observations will be assessed and weighted by dividing the number presented by number of non-missing and by multiplying by 28/66/68 for the joint count. No imputations for individual joints will be done. If a joint is not evaluable at Baseline, then that joint is set missing throughout the study.
- If data for more than 50% of the joints are missing at the time of a given assessment, then the total count will be set to missing for that visit.

Patient's Assessment of Arthritis Pain
• Subjects will assess the severity of their current arthritis pain using a continuous visual analogue scale (VAS) by placing a mark on the scale between "0" (no pain) and "10" (most severe pain), which corresponds to the magnitude of their current pain. • Subjects will also assess the severity of their past week's arthritis pain using a continuous visual analogue scale (VAS) by placing a mark on the scale between "0" (no pain) and "100" (severe pain), which corresponds to the magnitude of their pain for the past week. • The current endpoints are collected on eCRF after converted to a 100 unit. • No imputations for missing data will be done.
Patient's Global Assessment of Disease Activity
• Subjects will complete a global assessment of disease activity using the patient global assessment (PtGA) item, a continuous VAS with anchors "0" (very well) to "10" (very poor). • The current endpoints are collected on eCRF after converted to a 100 unit. • No imputations for missing data will be done.
Physician's Global Assessment of Arthritis
• Physicians will complete a global assessment of disease activity using the physician global assessment item (PhGA), a continuous VAS with anchors "0" (none) to "10" (extremely active). • The current endpoints are collected on eCRF after converted to a 100 unit. • No imputations for missing data will be done.

11.5.5. Immunogenicity

Immunogenicity
• Samples taken after dosing with GSK3196165 that have a value at or above the cut-point will be considered treatment emergent Anti-Drug-Antibody positive.

11.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as subjects who have completed all phases of the study including the following-up visit. • Withdrawn subjects were not replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.6.2. 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 : o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Binary variable	• Subjects with missing efficacy data or early withdrawal will be imputed as a failure (e.g. no DAS28(CRP) remission or no moderate/good EULAR response).
Continuous variable	• No imputation will be done.

11.6.2.1. Handling of Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Medications	• Missing start day, but month and year present: o If first study medication administration had been taken place in the same month and year as the occurrence of the medication, then the start day of the medication is assigned to the day of first study medication administration. o Otherwise the start day is set to the first day of the month (eg, XX-Sep-2010 is considered as 01-Sep-2010). • Missing start day and month, but year present: o If first study medication administration had been taken in the same year as the occurrence of the medication, then the start date of the medication is assigned to the date of first study medication administration. o Otherwise the start day and month is set to 01 January (eg, XX-XXX-2010 is considered as 01-Jan-2010). • Missing stop day, but month and year present: o The day is set to the last day of the month (eg, XX-Sep-2010 is considered as 30-Sep-2010). • Missing stop day and month, but year present: o The stop day and month is set to 31 December (eg, XX-XXX-2010 is considered as 31-Dec-2010). • The recorded partial date will be displayed in listings.
RA diagnosis and symptom onset	• Missing day, but month and year present: o Date is set to the first day of the month. • Missing day and month, but year present: o Date is set to 01 January.

11.6.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Continuous variables	• The analysis will be considered on the assumption of Missing at Random (MAR) (e.g. MMRM).

11.7. Appendix 7: Multiple Comparisons & Multiplicity

No multiplicity adjustment will be planned because no formal statistical hypotheses will be tested in this study.

11.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

11.8.1. Statistical Analysis Assumptions

Endpoint(s)	• Change from baseline in DAS28(CRP), DAS28(ESR), SDAI, CDAI and FACIT-fatigue
Analysis	• MMRM

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
  - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
- Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

Endpoint(s)	• Change from baseline in DAS28(CRP) at Week 12
Analysis	• Dose response analysis

- Distributional assumptions underlying the model used for analysis will be examined by obtaining a plot of the residuals versus the fitted values to gain confidence that the model assumptions are reasonable.

11.9. Appendix 9 – Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOCF	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
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11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.21	
Efficacy	2.1 to 2.37	2.1 to 2.26
Safety	3.1 to 3.38	
Pharmacokinetic	4.1 to 4.4	4.1 to 4.8
Pharmacodynamic and / or Biomarker	5.1 to 5.4	5.1 to 5.8
Pharmacokinetic / Pharmacodynamic		6.1 to 6.3
Section	**Listings**	
ICH Listings	1 to 77	

11.10.2. Deliverable

Delivery	Description
SAC	Final Statistical Analysis Complete

11.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ITT	ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.2.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.3.	All Screening	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.4.	All Screening	NS1	Summary of Subjects Enrolled by Site ID		SAC
Protocol Deviations					
1.5.	Randomised	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.6.	All Screening	SP1	Summary of Study Populations		SAC
1.7.	Randomised	SP2A	Summary of Exclusions from ITT Population		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
1.8.	ITT	DM1	Summary of Demographic Characteristics		SAC
1.9.	ITT	POP_T5	Summary of Baseline Efficacy Parameters		SAC
1.10.	ITT	POP_T6	Summary of Rheumatoid factor and Anti-Cyclic Citrullinated Protein Antibody		SAC
1.11.	All Screening	DM11	Summary of Age Ranges		SAC
1.12.	ITT	DM5	Summary of Race and Racial Combinations		SAC
1.13.	ITT	POP_T1	Summary of Substance Use		SAC
1.14.	ITT	POP_T2	Summary of Rheumatoid Arthritis Disease History		SAC
Prior and Concomitant Medications					
1.15.	ITT	CM1	Summary of Medications		SAC
1.16.	ITT	CM1	Summary of Medications for Rheumatoid Arthritis prior to the Date of first dose		SAC
1.17.	ITT	CM1	Summary of Medications for Rheumatoid Arthritis from the Date of first dose		SAC
1.18.	ITT	POP_T3	Summary of Oral Corticosteroid by Visit		SAC
1.19.	ITT	POP_T3	Summary of Change from Baseline in Oral Corticosteroid by Visit		SAC
Exposure					
1.20.	ITT	EX1	Summary of Exposure to Study Treatment		SAC
1.21.	ITT	POP_T4	Summary of Exposure to MTX		SAC

11.10.4. Efficacy Tables

Secondary Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS28(CRP)					
2.1.	ITT	EFF_T1	Summary of DAS28(CRP) Values		SAC
2.2.	ITT	EFF_T1	Summary of Change from Baseline in DAS28(CRP)		SAC
Statistical Analysis for DAS28(CRP) Comparison with Placebo					
2.3.	ITT	EFF_T2	Summary of Repeated Measures Analysis of Change from Baseline in DAS28(CRP)		SAC
Dose Response Analysis in DAS28(CRP)					
2.4.	ITT	EFF_T3 or EFF_T4	Summary of Results of Dose Response Analysis for Change from Baseline in DAS28(CRP) at Week 12	Statistician will select the final model among the three dose response models.	SAC

Exploratory Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ACR 20/50/70 response					
2.5.	ITT	EFF_T5	Summary of ACR 20 Responses		SAC
2.6.	ITT	EFF_T5	Summary of ACR 50 Responses		SAC
2.7.	ITT	EFF_T5	Summary of ACR 70 Responses		SAC
DAS28(ESR)					
2.8.	ITT	EFF_T1	Summary of DAS28(ESR) Values		SAC
2.9.	ITT	EFF_T1	Summary of Change from Baseline in DAS28(ESR)		SAC
2.10.	ITT	EFF_T2	Summary of Repeated Measures Analysis of Change from Baseline in DAS28(ESR)		SAC
SDAI, CDAI and FACIT-Fatigue					
2.11.	ITT	EFF_T1	Summary of SDAI Values		SAC
2.12.	ITT	EFF_T1	Summary of CDAI Values		SAC
2.13.	ITT	EFF_T1	Summary of FACIT-Fatigue		SAC
2.14.	ITT	EFF_T1	Summary of Change from Baseline in SDAI		SAC
2.15.	ITT	EFF_T1	Summary of Change from Baseline in CDAI		SAC
2.16.	ITT	EFF_T1	Summary of Change from Baseline in FACIT-Fatigue		SAC
2.17.	ITT	EFF_T2	Summary of Repeated Measures Analysis of Change from Baseline in SDAI		SAC
2.18.	ITT	EFF_T2	Summary of Repeated Measures Analysis of Change from Baseline in CDAI		SAC
2.19.	ITT	EFF_T2	Summary of Repeated Measures Analysis of Change from Baseline in FACIT-Fatigue		SAC

Categorical DAS28(CRP) / DAS28(ESR) Response					
2.20.	ITT	EFF_T5	Summary of Categorical DAS28(CRP) Responses		SAC
2.21.	ITT	EFF_T5	Summary of Categorical DAS28(ESR) Responses		SAC
DAS28(CRP) / DAS28(ESR) Remission					
2.22.	ITT	EFF_T5	Summary of DAS28(CRP) Remission		SAC
2.23.	ITT	EFF_T5	Summary of DAS28(ESR) Remission		SAC
The other endpoints					
2.24.	ITT	EFF_T6	Summary of Swollen/Tender Joint Counts		SAC
2.25.	ITT	EFF_T6	Summary of Patient's Assessment of Arthritis Pain		SAC
2.26.	ITT	EFF_T1	Summary of Patient's Global Assessment of Arthritis		SAC
2.27.	ITT	EFF_T1	Summary of Physician's Global Assessment of Arthritis		SAC
2.28.	ITT	EFF_T1	Summary of CRP		SAC
2.29.	ITT	EFF_T1	Summary of ESR		SAC
2.30.	ITT	EFF_T1	Summary of HAQ-DI score		SAC
2.31.	ITT	EFF_T6	Summary of Change from Baseline in Swollen/Tender Joint Counts		SAC
2.32.	ITT	EFF_T6	Summary of Change from Baseline in Patient's Assessment of Arthritis Pain		SAC
2.33.	ITT	EFF_T1	Summary of Change from Baseline in Patient's Global Assessment of Arthritis		SAC
2.34.	ITT	EFF_T1	Summary of Change from Baseline in Physician's Global Assessment of Arthritis		SAC
2.35.	ITT	EFF_T1	Summary of Change from Baseline in CRP		SAC
2.36.	ITT	EFF_T1	Summary of Change from Baseline in ESR		SAC
2.37.	ITT	EFF_T1	Summary of Change from Baseline in HAQ-DI score		SAC

11.10.5. Efficacy Figures

Secondary Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS28(CRP)					
2.1.	ITT	EFF_F3	Plot of Mean (95%CI) Change from Baseline in DAS28(CRP) Profiles		SAC
2.2.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in DAS28(CRP) Profiles		SAC
Statistical Analysis for DAS28(CRP) Comparison with Placebo					
2.3.	ITT	EFF_F3	Plot of Predicted (95%CI) Treatment Difference from Placebo in DAS28(CRP)		SAC
Dose Response Analysis in DAS28(CRP)					
2.4.	ITT	EFF_F2	Plot of Predicted (95%CI) Change from Baseline in DAS28(CRP) by the final Dose Response Model at Week 12	Statistician will select the final model among the three dose response models.	SAC
2.5.	ITT	EFF_F1	Plot of the Residuals versus the Predicted DAS28(CRP) by final Dose Response Model at Week 12		SAC

Exploratory Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ACR20/50/70					
2.6.	ITT	EFF_F4	Barplot of ACR20 Response Rate by Visit		SAC
2.7.	ITT	EFF_F4	Barplot of ACR50 Response Rate by Visit		SAC
2.8.	ITT	EFF_F4	Barplot of ACR70 Response Rate by Visit		SAC
DAS28(ESR)					
2.9.	ITT	EFF_F3	Plot of Mean (95%CI) Change from Baseline in DAS28(ESR) Profiles		SAC
2.10.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in DAS28(ESR) Profiles		SAC
Statistical Analysis for DAS28(CRP) Comparison with Placebo					
2.11.	ITT	EFF_F3	Plot of Predicted (95%CI) Treatment Difference from Placebo in DAS28(ESR)		SAC
SDAI, CDAI and FACIT-Fatigue					
2.12.	ITT	EFF_F3	Plot of Mean (95%CI) Change from Baseline in SDAI Profiles		SAC
2.13.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in SDAI Profiles		SAC
2.14.	ITT	EFF_F3	Plot of Mean (95%CI) Change from Baseline in CDAI Profiles		SAC
2.15.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in CDAI Profiles		SAC
2.16.	ITT	EFF_F3	Plot of Mean (95%CI) Change from Baseline in FACIT-Fatigue Profiles		SAC
2.17.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in FACIT-Fatigue Profiles		SAC

Exploratory Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Statistical Analyses for SDAI, CDAI and FACIT-Fatigue Comparisons with Placebo					
2.18.	ITT	EFF_F3	Plot of Predicted (95%CI) Treatment Difference from Placebo in SDAI		SAC
2.19.	ITT	EFF_F3	Plot of Predicted (95%CI) Treatment Difference from Placebo in CDAI		SAC
2.20.	ITT	EFF_F3	Plot of Predicted (95%CI) Treatment Difference from Placebo in FACIT-Fatigue		SAC
Each Components of Composite endpoints					
2.21.	ITT	EFF_F3	Plot of Mean (95% CI) Change from Baseline in CRP Profiles		SAC
2.22.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in CRP Profiles		SAC
2.23.	ITT	EFF_F3	Plot of Mean (95% CI) Change from Baseline in ESR Profiles		SAC
2.24.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in ESR Profiles		SAC
2.25.	ITT	EFF_F3	Plot of Mean (95% CI) Change from Baseline in HAQ-DI score Profiles		SAC
2.26.	ITT	EFF_F3	Plot of Median (Range) Change from Baseline in HAQ-DI score Profiles		SAC

11.10.6. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	ITT	AE1	Summary of All AEs by SOC and PT		SAC
3.2.	ITT	AE5A	Summary of All AEs by SOC and PT and Maximum Intensity		SAC
3.3.	ITT	SAFE_T4	Summary of AESI		SAC
3.4.	ITT	AE3	Summary of Adverse Events by Overall Frequency		SAC
3.5.	ITT	AE1	Summary of Drug-Related AEs by SOC and PT		SAC
3.6.	ITT	AE5A	Summary of Drug-Related AEs by SOC and PT and Maximum Intensity		SAC
3.7.	ITT	AE15	Summary of Common (>=5%) Non-Serious Adverse Events by SOC and PT		SAC
3.8.	ITT	AE1	Summary of AEs Leading to Withdrawal from Study		SAC
3.9.	ITT	AE1	Summary of AEs Leading to Permanent Discontinuation of Study Treatment		SAC
3.10.	ITT	SAFE_T4	Summary of AESI Leading to Permanent Discontinuation of Study Treatment		SAC
3.11.	ITT	AE1	Summary of Disease Related Events		SAC
Serious Adverse Events (SAEs)					
3.12.	ITT	AE16	Summary of Serious Adverse Events by SOC and PT		SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ECG					
3.13.	ITT	EG1	Summary of ECG Findings		SAC
3.14.	ITT	EG2	Summary of Change from Baseline in ECG Values by Visit		SAC
3.15.	ITT	EG2	Summary of ECG values by visit		SAC
Vital Signs					
3.16.	ITT	VS1	Summary of Change from Baseline in Vital Signs by Visit		SAC
3.17.	ITT	VS1	Summary of Vital Signs by Visit		SAC
Pulmonary					
3.18.	ITT	SAFE_T1	Summary of Cough by Visit and Grade		SAC
3.19.	ITT	SAFE_T1	Summary of Lung Auscultation by Visit		SAC
3.20.	ITT	SAFE_T2	Summary of Pulse Oximetry by Visit		SAC
3.21.	ITT	SAFE_T1	Summary of Borg Dyspnea Scale by Visit		SAC
3.22.	ITT	SAFE_T2	Summary of Percent Predicted Normal FEV1 by Visit		SAC
3.23.	ITT	SAFE_T2	Summary of Percent Predicted Normal FVC by Visit		SAC
3.24.	ITT	SAFE_T2	Summary of Percent Predicted HGB Corrected DLCO by Visit		SAC
3.25.	ITT	SAFE_T2	Summary of Change from Baseline in Pulse Oximetry by Visit		SAC
3.26.	ITT	SAFE_T2	Summary of Change from Baseline in Percent Predicted Normal FEV1 by Visit		SAC
3.27.	ITT	SAFE_T2	Summary of Change from Baseline in Percent Predicted Normal FVC by Visit		SAC
3.28.	ITT	SAFE_T2	Summary of Change from Baseline in Percent Predicted HGB Corrected DLCO by Visit		SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Respiratory events					
3.29.	ITT	SAFE_T5	Summary of Persistent cough, dyspnea and DLCO decrease by > 15%		SAC
Chemistry					
3.30.	ITT	LB1	Summary of Chemistry Changes from Baseline		SAC
3.31.	ITT	LB1	Summary of Chemistry by visit		SAC
3.32.	ITT	LB15	Summary of Emergent Chemistry Results Relative to Normal Ranges		SAC
Hematology					
3.33.	ITT	LB1	Summary of Hematology Changes from Baseline		SAC
3.34.	ITT	LB1	Summary of Hematology by Visit		SAC
3.35.	ITT	LB15	Summary of Emergent Hematology Results Relative to Normal Range		SAC
Urinalysis					
3.36.	ITT	UR3	Summary of Urinalysis Dipstick Results		SAC
Hepatobiliary (Liver)					
3.37.	ITT	LIVER10	Summary of Hepatobiliary Laboratory Abnomalities		SAC
Immunogenicity					
3.38.	Immunogenicity	SAFE_T3	Summary of Immunogenicity		SAC

11.10.7. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serum GSK3196165 Concentrations					
4.1.	PK	PK01	Summary of Serum GSK3196165 Concentrations		SAC
PK Parameters					
4.2.	PK	PK03	Summary of Derived Serum GSK3196165 Pharmacokinetic Parameters		SAC
4.3.	PK	PK05	Summary of Log-Transformed Derived Serum GSK3196165 Pharmacokinetic Parameters		SAC
4.4.	PK	PK_T1	Summary of Power Model Analysis for Dose Proportionality of GSK3196165 Pharmacokinetic Parameters	• Cmax • AUCtau • AUC(0-t) • AUC(0-inf)	SAC

11.10.8. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serum GSK3196165 Concentrations					
4.1.	PK	PK_F1	Individual Serum GSK3196165 Concentration-Time Plots (Linear and Semi-log)		SAC
4.2.	PK	PK17	Mean Serum GSK3196165 Concentration-Time Plots (Linear and Semi-log)		SAC
4.3.	PK	PK18	Median Serum GSK3196165 Concentration-Time Plots (Linear and Semi-log)		SAC
Parameters					
4.4.	PK	PK28	Plot of Individual Serum GSK3196196 Pharmacokinetic Parameters versus Dose	• Cmax • AUCtau • AUC(0-t) • AUC(0-inf)	SAC
4.5.	PK	PK_F2	Plot of GSK3196165 Pharmacokinetic Parameter Cmax vs. Treatment		SAC
4.6.	PK	PK_F2	Plot of GSK3196165 Pharmacokinetic Parameter AUCtau vs. Treatment		SAC
4.7.	PK	PK_F2	Plot of GSK3196165 Pharmacokinetic Parameter AUC(0-t) vs. Treatment		SAC
4.8.	PK	PK_F2	Plot of GSK3196165 Pharmacokinetic Parameter AUC(0-inf) vs. Treatment		SAC

11.10.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Biomarkers					
5.1.	ITT	PD1	Summary of Biomarkers	• free soluble GM-CSF • soluble GM-CSF complexed to GSK3196165 • MRP8/14 • ARGS neopitope • YKL-40 • 14-3-3η • IL-6 • IL-1β • TNFα • IL-17A • IL-17F	SAC
5.2.	ITT	PD3	Summary of Change from Baseline in Biomarkers	• free soluble GM-CSF • soluble GM-CSF complexed to GSK3196165 • MRP8/14 • ARGS neopitope • YKL-40 • 14-3-3η • IL-6 • IL-1β • TNFα • IL-17A • IL-17F	SAC

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety Biomarkers					
5.3.	ITT	PD1	Summary of Safety Biomakers	• SP-D • KL-6 • Cholestenoic Acid • GM-CSF Autoantibodies at Baseline	SAC
5.4.	ITT	PD3	Summary of Change from Baseline in Safety Biomarkers	• SP-D • KL-6 • Cholestenoic Acid	SAC

11.10.10. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Biomarkers					
5.1.	ITT	PD_F1	Plot of Mean Biomarkers	• free soluble GM-CSF • soluble GM-CSF complexed to GSK3196165 • MRP8/14 • ARGS neopitope • YKL-40 • 14-3-3η • IL-6 • IL-1β • TNFα • IL-17A • IL-17F	SAC
5.2.	ITT	PD_F2	Plot of Median Biomarkers	• free soluble GM-CSF • soluble GM-CSF complexed to GSK3196165 • MRP8/14 • ARGS neopitope • YKL-40 • 14-3-3η • IL-6 • IL-1β • TNFα • IL-17A • IL-17F	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
5.3.	ITT	PD_F1	Plot of Mean Change from Baseline in Biomarkers -Time Profile	• free soluble GM-CSF • soluble GM-CSF complexed to GSK3196165 • MRP8/14 • ARGS neopitope • YKL-40 • 14-3-3η • IL-6 • IL-1β • TNFα • IL-17A • IL-17F	SAC
5.4.	ITT	PD_F2	Plot of Median Change from Baseline in Biomarkers -Time Profile	• free soluble GM-CSF • soluble GM-CSF complexed to GSK3196165 • MRP8/14 • ARGS neopitope • YKL-40 • 14-3-3η • IL-6 • IL-1β • TNFα • IL-17A • IL-17F	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety Biomarkers					
5.5.	ITT	PD_F1	Plot of Mean Safety Biomarkers -Time Profile	• SP-D • KL-6 • Cholestenoic acid	SAC
5.6.	ITT	PD_F2	Plot of Median Safety Biomarkers -Time Profile	• SP-D • KL-6 • Cholestenoic acid	SAC
5.7.	ITT	PD_F1	Plot of Mean Change from Baseline in Safety Biomarkers -Time Profile	• SP-D • KL-6 • Cholestenoic acid	SAC
5.8.	ITT	PD_F2	Plot of Median Change from Baseline in Safety Biomarkers - Time Profile	• SP-D • KL-6 • Cholestenoic acid	SAC

11.10.11. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.1.	PK	PKPD_F1	Linear scatter plot of Change from Baseline in freesoluble GM-CSF level at each visit versus GSK3196165 concentration values at corresponding visit		SAC
6.2.	PK	PKPD_F1	Linear scatter plot of Change from Baseline in CRP levels at each visit versus GSK3196165 concentration values at corresponding visit		SAC
6.3.	PK	PKPD_F1	Linear scatter plot of Change from Baseline in DAS28(CRP) measures at each visit versus GSK3196165 concentration values at corresponding visit		SAC

11.10.12. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	ITT	ES2	Listing of Reasons for Subject Withdrawal		SAC
2.	ITT	SD2	Listing of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
3.	ALL Screening	ES7	Listing of Screening Status and Reasons for Screen Failure		SAC
4.	ALL Screening	ES9	Listing of Subjects Who Were Rescreened		SAC
5.	Randomised	BL1	Listing of Subjects Whom the Treatment Blind was Broken		SAC
6.	ITT	TA1	Listing of Planned and Actual Treatments	Sort by site id	SAC
Protocol Deviations					
7.	All Screening	DV2	Listing of Important Protocol Deviations		SAC
8.	All Screening	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
9.	ITT	SP3	Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
10.	ITT	DM2	Listing of Demographic Characteristics		SAC
11.	ITT	POP_L4	Listing of Rheumatoid factor and Anti-Cyclic Citrullinated Protein Antibody		SAC
12.	ITT	DM9	Listing of Race and Racial Combinations		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
13.	ITT	POP_L1	Listing of Substance Use		SAC
14.	ITT	POP_L2	Listing of Rheumatoid Arthritis Disease History		SAC
Prior and Concomitant Medications					
15.	ITT	MH2	Listing of Medical Conditions		SAC
16.	ITT	CM3	Listing of Medications		SAC
17.	ITT	CM6	Listing of Relationship of Medication Class, Dictionary Term and Verbatim Text		SAC
18.	ITT	SP1	Listing of Non-drug therapy		SAC
Exposure and Treatment Compliance					
19.	ITT	POP_L3	Listing of Exposure to Study Treatment		SAC
20.	ITT	EX3	Listing of Exposure to MTX		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
21.	ITT	AE8	Listing of All Adverse Events	Including the flag of whether each AE is related to GSK3196165/Placebo and/or Methotrexate	SAC
22.	ITT	SAFE_L1	Listing of Adverse Events of Special Interest – Serious Infections, and Non Serious Pulmonary or Opportunistic Infections		SAC
23.	ITT	SAFE_L1	Listing of Adverse Events of Special Interest – Systemic Hypersensitivity Reactions		SAC
24.	ITT	SAFE_L1	Listing of Adverse Events of Special Interest – Injection Site Reaction		SAC
25.	ITT	AE7	Listing of Subject Numbers for Individual AEs		SAC
26.	ITT	AE2	Listing of Relationship Between AE SOCs, PT and Verbatim Text		SAC
27.	ITT	AE8	Listing of Disease Related Events		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serious AE					
28.	ITT	AE8	Listing of Serious Adverse Events		SAC
ECG					
29.	ITT	CP_EG3	Listing of ECG values by Visit		SAC
30.	ITT	CP_EG5	Listing of Abnormal ECG Findings		SAC
Vital Signs					
31.	ITT	CP_VS4	Listing of Vital Signs by Visit		SAC
Pulmonary					
32.	ITT	SAFE_L2	Listing of Cough by Visit and Grade		SAC
33.	ITT	SAFE_L2	Listing of Lung Auscultation by Visit		SAC
34.	ITT	SAFE_L2	Listing of Pulse Oximetry by Visit		SAC
35.	ITT	SAFE_L2	Listing of Borg Dyspnea Scale by Visit		SAC
36.	ITT	SAFE_L2	Listing of Percent Predicted Normal FEV1 by Visit		SAC
37.	ITT	SAFE_L2	Listing of Percent Predicted Normal FVC by Visit		SAC
38.	ITT	SAFE_L2	Listing of Percent Predicted HGB Corrected DLCO by Visit		SAC
Respiratory events					
39.	ITT	SAFE_L5	Listing of Persistent cough, dyspnea and DLCO decrease by > 15%		SAC
Hepatic B Virus					
40.	ITT	SAFE_L3	Listing of HBV DNA monitoring		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Chemistry					
41.	ITT	LB5	Listing of Chemistry by Visit		SAC
Hematology					
42.	ITT	LB5	Listing of Hematology by Visit		SAC
Urinalysis					
43.	ITT	UR2a	listing of Emergent Urinalysis Dipstick Results		SAC
Immunogenicity					
44.	Immunogenicity	SAFE_L4	Listing of Immunogenicity		SAC
DAS28					
45.	ITT	EFF_L1	Listing of DAS28 Values	Including changes from baseline	SAC
ACR20/50/70					
46.	ITT	EFF_L2	Listing of ACR20/50/70	Including ACR components	SAC
Categorical DAS28 response / DAS28 remission					
47.	ITT	EFF_L3	Listing of Categorical DAS28 response		SAC
48.	ITT	EFF_L4	Listing of DAS28 remission		SAC
SDAI, CDAI and FACIT-Fatigue					
49.	ITT	EFF_L5	Listing of SDAI Values		SAC
50.	ITT	EFF_L5	Listing of CDAI Values		SAC
51.	ITT	EFF_L6	Listing of FACIT-Fatigue Values	Including FACIT-fatigue components	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Other endpoints					
52.	ITT	EFF_L7	Listing of Swollen/Tender Joint Count	include assessment status (Y or N or ND)	SAC
53.	ITT	EFF_L8	Listing of Patient's Assessment of Arthritis Pain		SAC
54.	ITT	EFF_L9	Listing of Patient's Global Assessment of Arthritis		SAC
55.	ITT	EFF_L9	Listing of Physician's Global Assessment of Arthritis		SAC
56.	ITT	EFF_L10	Listing of CRP		SAC
57.	ITT	EFF_L10	Listing of ESR		SAC
58.	ITT	EFF_L11	Listing of HAQ-DI score	Including HAQ-DI components	SAC
PK					
59.	PK	PK07	Listing of serum GSK3196165 concentration		SAC
60.	PK	PK_L1	Listing of GSK3196165 Pharmacokinetic parameters		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Biomarkers					
61.	ITT	PD10	Listing of Biomarkers	• free soluble GM-CSF • soluble GM-CSFcomplexed to GSK3196165 • MRP8/14 • ARGS neoepitope • YKL-40 • 14-3-3η • IL-6 • IL-1□ • TNF□ • IL-17A • IL-17F	SAC
Safety Biomarkers					
62.	ITT	PD10	Listing of Safety Biomarkers	• SP-D • KL-6 • Cholestenoic Acid • GM-CSF Autoantibodies	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Hepatobiliary (Liver)					
63.	ITT	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
64.	ITT	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		SAC
65.	ITT	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
66.	ITT	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score		SAC
67.	ITT	LIVER7	Listing of Liver Biopsy Details		SAC
68.	ITT	LIVER8	Listing of Liver Imaging Details		SAC
69.	ITT	JLE2	Listing of Laboratory Tests (Antigen and Antibody) for Liver Events		SAC
70.	ITT	JLE3	Listing of Laboratory Tests (DNA and RNA) for Liver Events		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Cardiovascular					
71.	ITT	EG5	Listing of ECG Findings in Cardiovascular Events		SAC
72.	ITT	SAFE_L (CV1)	Listing of Subjects who had Cardiovascular Events		SAC
73.	ITT	SAFE_L (CV2)	Listing of Diagnostic Test for Cardiovascular Events		SAC
74.	ITT	SAFE_L (FACV1)	Listing of Findings about Cardiovascular Events		SAC
75.	ITT	SAFE_L (HRU1)	Listing of Healthcare Resource Utilization due to Cardiovascular Events		SAC
76.	ITT	SAFE_L (NYHA1)	Listing of NYHA Functional Class for Cardiovascular Events		SAC
77.	ITT	SAFE_L (DTH1)	Listing of Death in Cardiovascular Events		SAC

11.10.13. Non-ICH listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Dose Response Analyses					
78.	ITT	EFF_L12	SAS Output of Dose Response Analysis of Change from Baseline in DAS28(CRP) using Emax model with 3 parameters		SAC
79.	ITT	EFF_L12	SAS Output of Dose Response Analysis of Change from Baseline in DAS28(CRP) using Emax model with 4 parameters		SAC
80.	ITT	EFF_L12	SAS Output of Dose Response Analysis of Change from Baseline in DAS28(CRP) using Linear model		SAC