PAREXEL International

GlaxoSmithKline

GSK Study 201755 (BAROQUE)

A Phase IIb, Double-Blind, Placebo-Controlled, Dose-Adaptive, Study of the Efficacy and Safety of GSK3196165 in Combination with Methotrexate Therapy, in Subjects with Active Moderate-Severe Rheumatoid Arthritis Despite Treatment with Methotrexate.

Reporting and Analysis Plan

PAREXEL Project Number: 220973

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SPONSOR SIGNATURE PAGE

PPD

Approved by: _____   16 DEC 2016

PPD   ave Inman   Date
            Principal Statistician
            GSK

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This document has been signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: Biostatistics Lead
Biostatistics Reviewer	PPD Project Role: Biostatistician
Statistical Programming Reviewer	Dr. PPD Project Role: Primary Statistical Programmer
Medical Writing Reviewer	PPD Project Role: Medical Writer

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-Drug-Antibody
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
AP	Actigraphy Population
ATC	Anatomical Therapeutic Chemical
BFI	Brief Fatigue Inventory
BLQ	Below the limit of quantification
BMI	Body Mass Index
BP	Bodily Pain
CfB	Change from Baseline
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CR	Compliance Ratio
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events v 4.0
DAS28	Disease activity score for 28 different joints
DAS28(CRP)	Disease activity score for 28 different joints with CRP value
DAS28(ESR)	Disease activity score for 28 different joints with ESR value
D_{LCO}	Diffusing capacity or transfer factor of the lung for carbon monoxide
DLCOHCPP	D_{LCO} Hemoglobin-corrected Percent of Predicted
DMARD	Disease modifying antirheumatic drugs
DRC	Data Review Committee
DRE	Disease-related Events
ECG	Electrocardiogram
eCRF	Electronic case report form
EOW	Every other week
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
EW	Early Withdrawal
F	Figure
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
FACIT	Functional Assessment of Chronic Illness Therapy
GEE	Generalized estimating equation
GH	General Health
GM-CSF	Granulocyte-macrophage colony stimulating factor
GRP	Genetic Research Population
GSK	GlaxoSmithKline
H0	Null Hypothesis
H1	Alternate Hypothesis
HAQ-DI	Health Assessment Questionnaire - Disability Index

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IA1	Interim Analysis 1
IA2	Interim Analysis 2
ITT	Intent-to-Treat
IV	Intravenous
L	Listing
LOCF	Last Observation Carried Forward
MCMC	Markov-Chain-Monte-Carlo
MCS	Mental Component Summary
MDRP	Medical Data Review Plan
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MH	Mental Health
MMP	Medical Monitoring Plan
MMRM	Mixed model for repeated measures
MTX	Methotrexate
NRI	Non-Responder imputation
NRS	Numeric rating scale
O	Supportive Analysis SAS Output
OC	Observed Case
PAP	Pulmonary alveolar proteinosis
PCS	Physical Component Summary
PD	Protocol deviation
PDS	Protocol deviation specification
PF	Physical Functioning
PFT	Pulmonary function tests
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PRO	Patient reported outcome
PT	Preferred term
PtGA	Patient's Global Assessment of Arthritis Disease Activity
QC	Quality Check
QTcF	Fridericia's Correction Formula
RA	Rheumatoid arthritis
RAP	Reporting and Analysis Plan
RE	Role Emotional
RP	Randomised Population
RPh	Role Physical
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDAI	Simplified Disease Activity Index
SC	Subcutaneous
SD	Standard deviation
SF	Social Functioning

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SF-36	Short-Form 36
SJC	Swollen joint count
SJC28	Swollen joint count for 28 different joints
SJC66	Swollen joint count for 66 different joints
SOC	System organ class
SOP	Standard Operating Procedure
SRT	Safety Review Team
STM	Set to Missing
T	Table
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TJC28	Tender joint count for 28 different joints
TJC68	Tender joint count for 68 different joints
VAS	Visual analogue scale
VT	Vitality

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1   INTRODUCTION

Rationale:
GSK3196165 is a novel human monoclonal anti-granulocyte-macrophage colony stimulating factor (GM-CSF) antibody that is being developed for the treatment of rheumatoid arthritis (RA).

This study is designed to provide the data necessary to select the optimal effective and safe dose(s) of GSK3196165 to be carried forward into Phase 3 studies in subjects with RA.

Rheumatoid Arthritis:
RA is a chronic, systemic inflammatory autoimmune disease, characterised by a symmetrical polyarthritis that is associated with substantial disability and morbidity.
Disease-modifying antirheumatic drugs (DMARDs) are the cornerstone of RA treatment throughout all stages of disease, and have been demonstrated to maintain or improve physical function and retard radiographic damage. This wide class of drugs includes conventional DMARDs, of which methotrexate (MTX) is the gold standard, and biological DMARDs which target cytokines, B-cells or T-cells. However, a substantial proportion of patients either fail to respond, or have inadequate response, to currently available RA therapies. Therefore, there is still a medical need for more effective treatments for RA with alternative mechanisms of action.

Intensive treatment (i.e. with a biologic drug) early in the disease course of RA, provides an opportunity to induce a sustained remission that can be maintained on conventional DMARDs alone thereby limiting the overall exposure to biological treatments during a patient's lifetime, which should translate into a better overall safety profile.

GM-CSF and RA:

Accumulating evidence suggests that the GM-CSF pathway may play a central role in the pathogenesis of RA, via the activation and differentiation of neutrophils and macrophages.

Taken together, pre-clinical and clinical data suggest that GM-CSF is a key mediator of inflammatory and immune disorders and central to RA pathogenesis, providing a strong rationale for considering it as a candidate for therapeutic intervention. Blocking GM-CSF should interfere with several pathophysiological pathways and significantly reduce inflammation by inhibiting activation of inflammatory cells and by blocking the chemotaxis of such cells into the joint thus inhibiting bone and cartilage destruction.

GSK3196165:

GSK3196165 is a high-affinity recombinant human monoclonal antibody that binds specifically to human GM-CSF and neutralises its biological function by blocking the interaction of GM-CSF with its cell surface receptor.

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Detailed information relating to non-clinical pharmacology, safety pharmacology, pharmacokinetics and metabolism, toxicology and other pre-clinical and clinical data with GSK3196165 can be found in the GSK3196165 Investigator's Brochure.

Contents of this document:

This document is based on the PAREXEL template for a Statistical Analysis Plan (SAP) and the following study documents:
- Clinical Study Protocol, Version 06 (effective date: 25-Nov-2015)
- electronic Case Report Form (eCRF) Blank Casebook, Version 3.0 (15-Sep-2015)
- Data Model Specification (TrialSlate) (16-Sep-2015)
- Population Pharmacokinetic Analysis of GSK3196165 Following Intravenous and Subcutaneous Administration to Healthy Volunteers, Subjects with Rheumatoid Arthritis and Multiple Sclerosis, (Date: 08-Jan-2016)

2   STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of GSK3196165	• Proportion of subjects who achieve disease activity score for 28 different joints with CRP value (DAS28(CRP)) remission (DAS28 <2.6) at Week 24.
Secondary	
To assess • Dose-efficacy response of GSK3196165 • Safety • Population pharmacokinetics • Pharmacodynamics • Novel biomarkers o To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to GSK3196165 and/or associated with the development or progression of RA or medically related conditions.	**Major Secondary Efficacy Endpoints** • Change from baseline in DAS28(CRP) at Week 12 (to support dose response evaluation). • Proportion of subjects achieving DAS28(CRP) remission at all assessment timepoints. • Change from baseline in DAS28(CRP) at all assessment timepoints. • Time to first DAS28(CRP) remission. • Proportion of subjects achieving categorical DAS28(CRP) response (moderate/good EULAR response) at all assessment timepoints. • ACR 20/50/70 response rates at all

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Objectives	Endpoints
	assessment timepoints.
	• Index- and Boolean-based ACR/EULAR remission rates, and CDAI remission rate at all assessment timepoints.
	• Change from baseline in SDAI and CDAI at all assessment timepoints.
	• Change from baseline in HAQ-DI score at all assessment timepoints.
	• Change from baseline in pain score at all assessment timepoints.
	• Change from baseline in physical and mental component scores and in domain scores of SF-36 at all assessment timepoints.
	• Change from baseline in FACIT-Fatigue at all assessment timepoints.
	• Change from baseline in BFI Question 3 at all assessment timepoints.
	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 (*e.g.*, graphically, as well as in Tables and Listings).
	Major Secondary Safety Endpoints
	• Incidence of adverse events and serious adverse events.
	• Incidence of infections.
	• Incidence of pulmonary events.

Exploratory
Efficacy Endpoints
• Proportion of subjects achieving sustained (≥24 continuous weeks including Week 52) DAS28(CRP) remission.
• Proportion of subjects achieving Major Clinical Response (proportion of subjects achieving ACR70 for ≥24 continuous weeks including Week 52).

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- DAS28(ESR) scores/responses at all assessment timepoints.

Pharmacokinetic/Pharmacodynamic Endpoints

- GSK3196165 pharmacokinetic parameters derived from serum concentration using sparse sampling.
- 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.* may include, but not limited to, 14-3-3η, MRP8/14, MMP-3, SAA).
- Pharmacodynamic biomarkers to assess response to GSK3196165 (*e.g.* may include, but not limited to, IL-6, IL-1β, TNFα, IL-17F, CCL17/Thymus and activation regulated cytokine).

Safety Biomarkers

- Serum biomarkers which may be indicative of lung damage (*e.g.* KL-6, LDH, SP-D, cholestenoic acid).
- Plasma biomarkers predictive of change in CYP3A4 activity.
- Baseline concentrations of GM-CSF autoantibodies.
- Immunogenicity.

Patient-Reported Outcomes

- Change over time and change from baseline in RA Symptom and Impact Diary measures.
- Change from baseline in BFI (Question 3) at Weeks 12, 24 and 52.

Actigraphy substudy at participating sites

To explore how actigraphy measurements of physical activity correlate to disease activity, the following measures will be explored as change over time and change from baseline:

- Inter- and intra-daily measures of physical activity including but not limited to:
  o Time spent sedentary (sitting and lying), time spent active (walking and standing), total activity score (function of duration and intensity of activity), number and duration of continuous walking periods.
  o Duration of morning stiffness.

- Measures of sleep quality including but not be limited to:
  o Time lying, number of movement episodes, sleep efficiency (function of % of movement time and total % of lying time) and fragmentation index (function of movement time % and number of movement episodes).

- RA Symptom and Impact Diary.

3   INVESTIGATIONAL PLAN

3.1   Overall Study Design and Plan

3.1.1   Overall Design

This is a randomised, Phase IIb, dose-adaptive, multicentre, double-blind, parallel group, placebo-controlled study with the primary objective to define the optimal therapeutic

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dose(s) of GSK3196165, in combination with MTX, in subjects with active moderate-severe RA despite treatment with MTX.

Approximately 210 subjects will be randomised into the study, following a screening period of up to four weeks. The total treatment period is up to 52 weeks, with a 12-week follow-up period after the last dose (Week 50).

In order to facilitate a sub-analysis of subjects with early RA (who may have greater benefit of treatment), the study aims to recruit up to approximately 40% of subjects with RA disease duration of <2 years, however the actual proportion of subjects required will be assessed throughout the study. A subgroup analysis of subjects with early RA will be performed if this subgroup accounts for at least 10% of subjects.

The study schematic is as shown below:

Study design - 52 week combination dosing with dose escalation for subjects with insufficient response at Week 12 and Week 24, with a withdrawal point at Week 36 and with a 12-week follow-up visit after the last dose (Week 50):

[a] Escape at W12:
Placebo, 22.5 mg, 45 mg, 90 mg or 135 mg. Subjects that fail to achieve EULAR good or moderate response at W12, escalate to 180 mg (or the highest remaining dose) for remainder of study from W14
[b] Escape at W24:
Placebo, 22.5 mg, 45 mg, 90 mg or 135 mg. Subjects that remained on their original randomised dose, with DAS28 >3.2 at W24, escalate to 180 mg (or the highest remaining dose) for remainder of study from W26
[c] Mandatory withdrawal point:
Any subject not achieving EULAR good/moderate response at W36 will be withdrawn from the study at W38

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Study visits:

Screening assessments (Visit 1) will be performed up to 28 days prior to the baseline visit (Visit 2) on Day 1 (start of study treatment). Subsequent visits are planned on Days 3, 8, 15, 22, 29 (=Week 4) and then every other week (EOW) in weeks 6 through 52, with a follow-up visit in Week 62. Subjects who discontinue the study treatment should have an early withdrawal visit with a subsequent follow-up visit ≥12 weeks after the last dose of study treatment. The exact timing of each assessment is listed in the Time and Events Table in section 3.1.2.

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3.1.2 Time and Events Table (Combination Treatment with GSK3196165 and MTX)

Table 1 Time and Events Table

Procedures	Screening - up to 4 weeks	Baseline																														FU	EW[1]
Week				1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	62	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
Day[21]	-7	1	3*	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351	365	435	
Written Informed Consent(s)	X																																	
Subject Demography	X																																	
Medical, Disease, Therapy History	X																																	
Inclusion/Exclusion Criteria	X																																	
Efficacy[2] and PRO Assessments[3]																																		
Swollen (66) & Tender (68) Joint Count[2]	X		X[4]	X	X		X	X	X		X		X		X		X		X		X		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		X		X		X		X		X		X		X		X	X	X	X
HAQ-DI[3]	X		X[4]	X	X		X	X	X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
BFI Question 3, FACIT-Fatigue, SF-36 (acute v2)[3]			X[4]					X					X						X						X						X	X	X	X
RA Symptom and Impact Diary[3,5]			X[4]	X									X						X						X						X	X		X

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Procedures	Screening - up to 4 weeks	Baseline	3*	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351	365	FU	EW1
Week (Treatment Period)				1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	62	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
Day	-7	1	3*	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351	365	435	
RA Symptom and Impact Diary, Actigraphy process[3,6]	X[7]			X[8]							X[7]	X[8]					X[7]	X[8]					X[7]	X[8]							X[7]	X[8]		X[8]
Safety Evaluations[9]																																		
Concomitant Medication	X	X[4]	Record all concomitant medications →																															
Physical Examination[10], Vital Signs	X[4]	X	X	X			X			X			X			X			X			X			X			X			X	X	X
12-lead ECG[11]	X										X						X															X	X
AEs/SAEs/AESI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray[12]	X																																
Spirometry (FEV1, FVC)	X	X[4]									X						X						X								X	X	X
D$_{LCO}$	X[13]	X[4,14]									X						X						X								X	X	X
Laboratory Assessments																																		
Hematology, Chemistry	X	X[4]			X		X		X		X		X			X					X					X					X	X	X
Urinalysis (dip stick)	X						X		X		X		X			X					X					X					X	X	X
Cholesterol, triglycerides, HDL, LDL[15]		X[4]									X						X														X	X	X
Pregnancy test[16]	S	U							U		U		U		U		U		U		U		U		U		U		U		U	U	U
TB, HBsAg, Hep B cAb, HepC Ab, HIV	X																																
RF, ACPA (anti-CCP)	X																																

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Procedures	Screening (Day -7)	Baseline (Day 1)	3*	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351	365	FU (Day 435)	EW[1]
Week				1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	62	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
CRP, ESR[17]	X	X[4]		X	X		X	X	X		X		X		X		X		X		X		X		X		X		X		X	X	X
Other Laboratory Assessments																																	
PK Sampling (GSK3196165)[18]		X[4]	X*	X	X		X		X		X		X		X		X						X								X	X	X
GM-CSF & PD blood biomarkers		X[4]	X*	X	X		X		X		X						X						X								X	X	X
PGx sampling RNA[19]		X[4]									X						X						X								X	X	X
PGx sampling DNA[19]		X[4]																															
Lung biomarkers[20]		X[4]									X						X						X								X	X	X
Cholesterol/4β-hydroxycholesterol		X[4]									X																						
Immunogenicity[21]		X[4]			X		X				X						X						X								X	X	X
Anti-GM-CSF auto-antibodies[20]		X[4]																															
Study Treatment GSK3196165/placebo[22] (Methotrexate and folic acid weekly throughout treatment with GSK3196165)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Rescue point for possible dose escalation												X							X														
Decision point for mandated withdrawal[23]																								X									

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1. All subjects who discontinue study medication prematurely should have an early withdrawal (EW) visit as soon as possible after study agent discontinuation and then return for a follow-up safety visit at least 12 weeks after last dose of study medication.
2. The same individual (where possible) should perform all disease assessments for an individual subject (with separate joint assessor).
3. All 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 24 hours before dosing GSK3196165.
5. Non-actigraphy sub-study subjects only.
6. Performed in a subset of consenting subjects only.
7. Actigraphy device placed and tagging process started (as detailed in the SRM), RA Symptom and Impact Diary questionnaire started on the same day at home using an electronic PRO (ePRO) device and completed on a daily basis until next visit.
8. Actigraphy device collected and RA Symptom and Impact Diary questionnaire completed at site visit and ePRO device collected.
9. All safety evaluations should be conducted before dosing GSK3196165.
10. Complete physical at baseline, and then limited physical examination (abdominal examination and heart sounds) thereafter.
11. ECG should be performed before vital signs, blood draws, and dosing.
12. Unless performed within previous 12 weeks (No need to repeat if subject re-screened).
13. Chest HRCT if D_{LCO} ≥60% - <70% predicted (No need to repeat if subject re-screened).
14. If the screening D_{LCO} value is ≥70% predicted, but the subsequent "Day 1" value is <70 but ≥60% predicted, the D_{LCO} test must be repeated if still within the screening window. If the repeat value is ≥70%, the "Day 1" activities may be completed, but if the value is again <70%, dosing must be postponed and a chest HRCT performed. If this cannot be done within the screening window then the subject must be re-screened.
15. >8h fasting required before blood draw.
16. For women of child-bearing potential. S=serum; U=urine.
17. ESR measured locally.
18. Blood samples taken before dosing GSK3196165.
19. In consenting subjects.
20. To be analysed at end of study or in event of pulmonary safety signal.
21. In addition to these scheduled immunogenicity assessments, "event-driven" testing will also be employed for those subjects that experience anaphylaxis, serious hypersensitivity, or adverse events related to study drug administration that led to withdrawal from the study.
22. 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.
23. Any subject not achieving EULAR good/moderate response at Week 36 will be withdrawn from the study at Week 38.
*   The Day 3 blood sample may be drawn ±1 day.

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3.1.3 Treatment Arms and Duration

In the "dose selection" component of the study, subjects will be randomised (1:1:1:1:1:1) to placebo or one of five subcutaneous GSK3196165 doses, in combination with MTX (at a dose between 15-25 mg previously received for at least 12 weeks, with a stable and tolerated dose and route of administration for ≥4 weeks).

Treatment with GSK3196165 will be given as a single subcutaneous (SC) injection by an unblinded administrator (shielded to subjects) weekly for 5 injections (Days 1, 8, 15, 22, 29), then EOW thereafter beginning at Day 43 (Week 6).

GSK3196165/placebo must be administered on the same day each week ±1 day for the first 5 weekly doses. Following this GSK3196165/placebo must be administered on the same day EOW ±3 days.

After the Day 85 (Week 12) administration:

- "Escape therapy" is provided for all subjects not on the 180 mg dose:

  - Subjects in the placebo, 22.5 mg, 45 mg, 90 mg and 135 mg arms will be escalated in a double-blind fashion to the 180 mg (or the highest remaining) dose at Week 14 if they have failed to achieve European League against Rheumatism (EULAR) good/moderate response (see section 3.2.1) at Week 12.

  - Subjects in these groups who do not meet this criterion and therefore do not escalate therapy at Week 14 have another opportunity for "escape" at Week 24 with escalation in a double-blind fashion to the 180 mg (or the highest remaining) dose at Week 26 if their DAS28(CRP) score at this timepoint is >3.2.

This escape requirement is based on EULAR guidance and a review of response to MTX in randomised clinical studies.

Any subject that does not achieve EULAR good/moderate response at Week 36 will not be dosed at Week 38, and will be withdrawn from the study.

3.1.4 Study Oversight and Dose Selection

A Data Review Committee (DRC) consisting of external rheumatology, infectious disease and respiratory experts, and GSK study team members that have no involvement in the acquisition of the data or direct contact with sites, will review ongoing unblinded safety data from the study and unblinded efficacy data at the interim analyses.

Pharmacokinetic (PK) concentration time data will be presented to DRC only if required to aid the interpretation of the efficacy or safety data.

The first DRC review of safety data will be conducted after approximately 10 subjects per arm have completed 5 weeks of treatment, and subsequent reviews will take place approximately every 12 weeks thereafter until the end of the study. The recommendation to stop the study or randomisation to specific arms will be made by the DRC and ratified by the GSK steering committee consisting of senior GlaxoSmithKline Pharmaceuticals, R&D leaders.

Interim analyses will be performed to assess futility and the dose-efficacy relationship when 90 subjects have completed 4 and 12 weeks of treatment. If the recruitment rates allow, these

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interim analyses will be aligned with safety reviews to allow an assessment of benefit versus risk. Based on these interim analyses, the overall efficacy and the dose-response model will be defined and the effective therapeutic dose(s) of GSK3196165 selected. New subjects will be randomised to the dose(s) identified, which will be from the dose range already studied, with the maximum dose not exceeding 180 mg. If there is no evidence of efficacy, the study could also be stopped for futility.

There will be no pause in recruitment whilst the review of safety data or interim analyses is conducted.

Once the effective therapeutic dose(s) have been selected at the interim analyses, treatment allocation could be adapted so that randomisation is stopped to the ineffective doses and future subjects are randomised to only the effective dose(s) and placebo. Subjects already in the study will remain on the arm to which they were randomised. There is a rescue option for all subjects, whereby the subjects can be escalated to the highest remaining dose for the remainder of the study. The randomisation ratio will be 1:1:1:1:1:1 across the original 6 arms of the study (*i.e.*, n=35 in each dosing group). However, due to the re-allocation of subjects once the effective dose(s) are known, it is likely that at the end of the study there will be more subjects in the effective dose groups and placebo.

Medical monitoring will happen in the form of monthly blinded data review meetings which include but are not limited to:

- Medical review of protocol deviations
- Medical review of high panic lab alerts
- Cumulative data review (includes summaries of reason for screening failures, disposition, adverse events, serious adverse events, disease related events and chest x-rays)
- Medical review of coding

Further information on the medical monitoring can be found in the Medical Data Review Plan (MDRP) and the Medical Monitoring Plan (MMP).

The primary analysis will occur 24 weeks after the last subject was randomised. The final analysis will occur after the end of the study which is defined as the last subject's last visit.

3.1.5   Type and Number of Subjects

Approximately 350 subjects with active moderate-severe RA despite treatment with MTX will be screened (subjects can be rescreened once) to achieve 210 randomised.

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3.2   Efficacy and Safety Variables

3.2.1   Disease Activity Score (DAS):

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 Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst)

DAS28(CRP)

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

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

If one of the components is missing at an individual assessment point, the DAS28(CRP) value for that assessment will be set to missing. An alternative imputation method for missing components will be applied as described in Section 4.5.2.

DAS28(ESR)

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

$$\text{DAS28(ESR)} = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.7 * \ln(\text{ESR}) + 0.014 * \text{PtGA}$$

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).

DAS28 Remission

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

Sustained DAS28(CRP) Remission

Sustained DAS28(CRP) remission is achieved if DAS28(CRP) remission is achieved (i.e. "response" in the Non-Responder imputation [NRI] dataset) at every visit within a period of time

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that spans at least 24 weeks (168 days) and includes the Week 52 visit. This is a change from the protocol defined endpoint. If a subject has at most two nonconsecutive visits with missing remission data ("no response" in the NRI dataset due to a missed visit or missing DAS28(CRP) component scores) within the 24 week window and the subject was in remission ("response" in the NRI dataset) for all other visits, then the subject will be considered to have sustained remission. Otherwise, two consecutive visits of missing data or more than two visits of missing data in a 24 week window will disqualify the subject for sustained remission.

Two variables will be determined for each subject (not by visit):
- Subject reached sustained DAS28(CRP) remission (yes/no)
- The duration of sustained DAS28(CRP) remission in weeks.

Categorical DAS28 Response

DAS28(CRP) and DAS28(ESR) scores will each be categorised using EULAR response criteria. Response at a given time point is defined based on the combination of current DAS28 score and the improvement in the current DAS28 score relative to baseline. The definition of no response, moderate response and good response is captured in the following table:

Table 2 EULAR Response Criteria

Current	DAS28 decrease from baseline value		
DAS28	>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) score is missing, then the corresponding EULAR category will be missing.

3.2.2   ACR Response Rates

The American College of Rheumatology's (ACR) definition for calculating improvement in RA is calculated as a 20% improvement (ACR20) in both tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, patient's assessment of arthritis pain, disability, and an acute-phase reactant (i.e. CRP value). Similarly, ACR50 and ACR70 are calculated with the respective percent improvement. This efficacy measurement will be made at every post-baseline study assessment time point.

The specific components of the ACR Assessments that will be used in this study are:

- Tender/Painful Joint count 68 (TJC68)
- Swollen Joint Count 66 (SJC66)
- Patient's Assessment of Arthritis Pain
- Patient's Global Assessment of Arthritis Disease Activity

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- Physician's Global Assessment of Arthritis
- CRP (mg/L)
- Health Assessment Questionnaire – Disability Index (HAQ-DI)

For all visits, if any of the component scores are missing, then those scores will be 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" in the NRI dataset.

For component scores with missing Baseline values or a Baseline value of 0, the percentage improvement can't be calculated and the component will be considered as not having met the criteria for improvement for all visits. If the baseline value is missing, do not use screening visit data for imputation.

Major clinical response is achieved if ACR70 is achieved (i.e. "response" in the NRI dataset) at every visit within a period of time that spans at least 24 weeks (168 days) and includes the Week 52 visit. This is a change from the protocol defined endpoint. If a subject has at most two nonconsecutive visits with missing ACR70 response data ("no response" in the NRI dataset due to a missed visit or missing ACR component scores) within the 24 week window and the subject had ACR70 response ("response" in the NRI dataset) for all other visits, then the subject will be considered to have achieved major clinical response. Otherwise, two consecutive visits of missing data or more than two visits of missing data in a 24 week window will disqualify the subject for major clinical response.

3.2.3   Swollen and Tender/Painful Joint Count

Four different scores will be calculated to evaluate swelling and tenderness of joints. TJC28 and SJC28 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 SJC66/TJC68:
Temporomandibular (2), Sternoclavicular (2), Acromioclavicular (2), Fingers (DIP: 8), Ankle (2), Tarsus (2), Toes (PIP, MTP: 20), Hip (2, only for TJC).
Artificial, ankylosed and missing joints are excluded from swelling and tenderness assessment.

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

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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 to 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.

Observed joint states will be listed without any modification for every subject and visit.

3.2.4 Patient's Assessment of Arthritis Pain

Subjects will assess the severity of their current arthritis pain using a continuous visual analog scale (VAS) with anchors "0" (no pain) and "100" (most severe pain).

No Imputations for missing data will be done.

3.2.5 Patient's Global Assessment of Disease Activity

Subjects will complete a global assessment of disease activity using the patient global assessment of disease activity (PtGA) item, a continuous VAS with anchors "0" (very well) to "100" (very poor).

No imputations for missing data will be done.

3.2.6 Physician's Global Assessment of Arthritis

Physicians will complete a global assessment of disease activity using the physician global assessment of disease activity item (PhGA), a continuous VAS with anchors "0" (none) to "100" (extremely active).

No imputations for missing data will be done.

3.2.7 SDAI

The Simple Disease Activity Index (SDAI) is a composite score consisting of the sum of SJC28, TJC28, PtGA/10, PhGA/10, and CRP (mg/dl). Higher values represent higher disease activity.

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

3.2.8 CDAI
The Clinical Disease Activity Index (CDAI) is a composite score consisting of the sum of SJC28, TJC28, PtGA/10, PhGA/10. CDAI ranges from 0 to 76 with higher values representing higher disease activity. Remission is achieved for a non-missing CDAI value ≤ 2.8.

If one of the components is missing at an individual assessment point, no imputations will be done and the CDAI value for that assessment will be set to missing.

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3.2.9   Index- and Boolean-based ACR/EULAR Remission Rates

Boolean-based remission (Felson, 2011) is achieved if all of the following requirements are met at the same time:

- TJC68 $\leq$ 1
- SJC66 $\leq$ 1
- CRP $\leq$ 1mg/dl
- PtGA $\leq$ 10

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

Index-based remission is achieved if the following requirement is met:

- SDAI $\leq$ 3.3

If the SDAI value is missing at an individual assessment point, Index-based remission for that assessment will be set to missing.

3.2.10   HAQ-DI

The functional status of the subject will be assessed by means of the Disability Index of the Stanford Health Assessment Questionnaire (HAQ-DI). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas:

- dressing & grooming, rising, eating, walking, hygiene, reach, grip, and common daily 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 equipment	Will be associated with category score
Walking stick/frame, crutches, wheelchair	Walking
Aids used for dressing	Dressing and grooming
Specially adapted utensils	Eating
Specially adapted chair	Rising
Raised toilet seat, bath rail, bath seat	Hygiene
Long-handled appliance in bathroom	Hygiene
Long-handled appliance for reaching	Reach
Jar opener	Grip
Other (1)	Dressing & grooming, rising, eating, walking

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Other (2)	hygiene, reach, grip, common daily activities

If "other" is marked as an aid or equipment then this can be assigned to a group of four functional areas and will be handled as an aid or equipment for each of the four functional areas. Therefore, if the maximum score of a functional area is 0 or 1 that value is increased to a score of 2 for each of the four functional areas.

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.

Severity of pain within the past week is also assessed by the HAQ-DI questionnaire but will not be considered for calculating the HAQ-DI score. Severity of pain will not be included in summaries but will be listed.

3.2.11 Short-Form 36

Health-related quality of life will be assessed using the subject-completed Medical Outcomes Study Short-Form 36 (SF-36) which is a generic health survey that contains 36 questions covering eight domains of health. The SF-36 yields an eight-scale profile of functional health and well-being scores as well as physical and mental component health summary scores. The version 2, 1-week recall questionnaire will be used. Recoding, calculations and standardisation will be done as recommended in the User's manual for the SF-36 (Maruish, 2011).

3.2.11.1 Domain Scores of SF-36

Each of the 8 domain scores is the sum of some of the overall 36 item scores.

Item	Abbreviated Item Content
Item 1	Health
Item 2	Health now compared to 1 week ago
Item 3a	Health limits vigorous activities
Item 3b	Health limits moderate activities
Item 3c	Health limits lifting or carrying groceries
Item 3d	Health limits climbing several flights of stairs
Item 3e	Health limits climbing one flight of stairs
Item 3f	Health limits bending, kneeling or stopping
Item 3g	Health limits walking more than mile
Item 3h	Health limits walking several hundred yards
Item 3i	Health limits walking one hundred yards

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Item 3j	Health limits bathing or dressing
Item 4a	Cutting work time due to physical health
Item 4b	Accomplishing less due to physical health
Item 4c	Limited in kind of work due to physical health
Item 4d	Difficulty performing work due to physical health
Item 5a	Cutting work time due to emotional problems
Item 5b	Accomplishing less due to emotional problems
Item 5c	Less carefully due to emotional problems
Item 6	Physical health/emotional problems interfere with social activities (extent)
Item 7	Bodily Pain
Item 8	Pain interferes with work
Item 9a	Full of Life
Item 9b	Nervous
Item 9c	Down in the dumps
Item 9d	Calm and peacefully
Item 9e	Lot of energy
Item 9f	Downhearted and low
Item 9g	Worn out
Item 9h	Happy
Item 9i	Tired
Item 10	Physical health/emotional problems interfere with social activities (frequency)
Item 11a	Getting ill more easily than other people
Item 11b	As healthy as anybody
Item 11c	Expecting health to get worse
Item 11d	Excellent health

For every one of the items, the answers will be rated in a way such that higher values will be associated with higher health-related quality of life (see ratings below).

Rating of the item answers:

Item 1:

Answer	Excellent	Very Good	Good	Fair	Poor
Value	5.0	4.4	3.4	2.0	1.0

Item 2:

Answer	Much better now	Somewhat better now	About the same	Somewhat worse	Much worse
Value	1	2	3	4	5

Item 2 is not used for the calculation of any of the 8 domain scores.

Items 3a-3j:

Answer	Yes, limited a lot	Yes, limited a little	No, not limited at all
Value	1	2	3

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Items 4a-4d and 5a-5c:

Answer	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Value	1	2	3	4	5

Item 6:

Answer	Not at all	Slightly	Moderately	Quite a bit	Extremely
Value	5	4	3	2	1

Item 7:

Answer	None	Very mild	Mild	Moderate	Severe	Very severe
Value	6.0	5.4	4.2	3.1	2.2	1.0

Item 8 is recoded depending on whether item 7 is answered or not:

Original Answer item 8	Not at all	Not at all	A little bit	Moderately	Quite a bit	Extremely
Answer item 7	Very severe	None, Very mild, Mild, Moderate, Severe	None, Very mild, Mild, Moderate, Severe, Very severe	None, Very mild, Mild, Moderate, Severe, Very severe	None, Very mild, Mild, Moderate, Severe, Very severe	None, Very mild, Mild, Moderate, Severe, Very severe
Value item 8	6	5	4	3	2	1

Original Answer item 8	Not at all	A little bit	Moderately	Quite a bit	Extremely
Answer item 7	NA	NA	NA	NA	NA
Value item 8	6.0	4.75	3.5	2.25	1.0

Items 9a, 9d, 9e, 9h:

Answer	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Value	5	4	3	2	1

Items 9b, 9c, 9f, 9g, 9i and 10:

Answer	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Value	1	2	3	4	5

Items 11a and 11c:

Answer	Definitely true	Mostly true	Don´t know	Mostly false	Definitely false
Value	1	2	3	4	5

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Items 11b and 11d:

Answer	Definitely true	Mostly true	Don´t know	Mostly false	Definitely false
Value	5	4	3	2	1

The initial domain scores are the sum of individual item scores:

General Health (GH)
GH = 1 + 11a + 11b + 11c + 11d

Physical Functioning (PF)
PF = 3a + 3b + 3c + 3d + 3e + 3f +3g + 3h + 3i + 3j

Role Physical (RPh)
RPh = 4a + 4b + 4c + 4d

Role Emotional (RE)
RE= 5a + 5b + 5c

Social Functioning (SF)
SF = 6 + 10

Bodily Pain (BP)
BP = 7 + 8

Vitality (VT)
VT = 9a + 9e + 9g + 9i

Mental Health(MH)
MH = 9b + 9c + 9d + 9f + 9h

Imputation
Domain scores will only be calculated if less than half of the item scores are missing. Missing item scores will be imputed as the mean of the other item scores within the same domain. If at least half of the item scores of a domain are missing, imputation will not be performed and the domain will be set to missing.

Standardisation
All raw domain scores will be transformed on a 0–100 scale (transformed domain scores) and then standardised into norm-based scores:

Transformed domain score = 100 x (Actualraw score – lowest possible raw score) / (highest possible raw score – lowest possible raw score)

One example would be:

$$PF\_S = 100 * (PF - 10)/(30 - 10)$$

Each transformed domain score is standardised using a z-score transformation. Z-scores are computed by subtracting the health domain scale's 2009 U.S. general population mean from the

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0–100 score for that scale, and then dividing the difference by the given scale's standard deviation:

$PF\_Z = (PF\_S – 83.29094) / 23.75883$

$RPh\_Z = (RPh\_S – 82.50964) / 25.52028$

$BP\_Z = (BP\_S – 71.32527) / 23.66224$

$GH\_Z = (GH\_S – 70.84570) / 20.97821$

$VT\_Z = (VT\_S – 58.31411 / 20.01923$

$SF\_Z = (SF\_S – 84.30250) / 22.91921$

$RE\_Z = (RE\_S – 87.39733) / 21.43778$

$MH\_Z = (MH\_S – 74.98685) / 17.75604$

The next step is the transformation of each z-score to a norm-based score using a t-score transformation (Mean=50, Standard Deviation (SD) =10) and the following formulas:

$PF\_N = 50 + (PF\_Z * 10)$

$RPh\_N = 50 + (RPh\_Z * 10)$

$BP\_N = 50 + (BP\_Z * 10)$

$GH\_N = 50 + (GH\_Z * 10)$

$VT\_N = 50 + (VT\_Z * 10)$

$SF\_N = 50 + (SF\_Z * 10)$

$RE\_N = 50 + (RE\_Z * 10)$

$MH\_N = 50 + (MH\_Z * 10)$

These norm-based values (e.g. PF_N) are the final domain scores and will be used in summary tables. The raw values (e.g. PF), the standardised values (e.g. PF_S) and the final scores (e.g. PF_N) will be shown in a listing for every subject and visit.

3.2.11.2 Physical and Mental Component Scores

Following the transformation of the eight domain scores into z-scores, the Mental Component Summary (MCS) and the Physical Component Summary (PCS) are aggregated using weights from the 1990 US general population:

$AGG\_PHYS = (PF\_Z * 0.42402) + (RPh\_Z * 0.35119) + (BP\_Z * 0.31754) + (GH\_Z * 0.24954) + (VT\_Z * 0.02877) + (SF\_Z * -0.00753) + (RE\_Z * -0.19206) + (MH\_Z * - 0.22069)$

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AGG_MENT = (PF_Z * -0.22999) + (RPh_Z * -0.12329) + (BP_Z * -0.09731) + (GH_Z * -0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876) + (RE_Z * 0.43407) + (MH_Z * 0.48581)

Finally, each component score is transformed to norm-based scoring using the following formulas:

Transformed Physical Score: PCS = 50 + (AGG_PHYS * 10)
Transformed Mental Score: MCS = 50 + (AGG_MENT * 10)

Component scale scores (PCS and MCS) will be set to missing if the subject is missing any one of the eight SF-36 scales.

While the norm-based scores are calculated such that the mean ± SD of these scores in the US general population is 50 ± 10, the lowest and highest possible scores for the PCS are 1 and 81, respectively. For the MCS, the lowest and highest possible scores are -9 and 82, respectively.

3.2.12 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) -fatigue questionnaire is a patient-reported measure developed to assess fatigue consisting of 13 statements regarding feeling fatigue using a numeric rating scale (NRS) ranging from 0 to 4. 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 (i.e. a better quality of life).

If more than 6 individual items are missing at an assessment the FACIT-Fatigue score will be set to missing at that assessment.

3.2.13 BFI

Brief Fatigue Inventory (BFI) is a self-reported instrument consisting of nine questions which correlate well with quality-of-life measures. For this study, Question 3 only will be used which asks about fatigue severity at its worst in the last 24 hours.
A discrete 11 unit NRS will be used where 0 is "No fatigue", and 10 is "As bad as you can imagine".

No imputations will be done for missing data.

3.2.14 Borg Dyspnea Scale

The Borg dyspnea scale will be used to assess dyspnea. A discrete 18 unit scale will be used ranging from "Nothing at all" to "Absolute maximum".

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No imputations will be done for missing data.

4   STATISTICAL METHODS

4.1   Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2   General Presentation Considerations

For each subject 'Baseline' is defined as the last available assessment prior to the start of study treatment. For Efficacy variables no Screening information will be used for Baseline.   For DLCO, separate Baseline rules are defined in section 4.10.9. For each subject 'End of Study' is defined as the last available assessment which is on or after the day of last study treatment.

The relative study day will be included in adverse event data, medical history and concomitant medication listings, and will be calculated as follows:

- Relative Day 1 is the date of first study medication administration.
- Relative Day of date X = date X - Date of first study medication administration + 1 if date X is on or after date of first study medication administration.
- Relative Day of date X = date X - Date of first study medication administration if date X is before date of first study medication administration.

Relative days before first study medication administration will have the prefix "-". Additionally for relative days after last study medication administration, the number of days since last study medication administration will be presented with the prefix "+". Calculations of "Relative Day" will not include partial dates, but will be left blank in listings.

According to the design the study can be split into 5 time periods:

- Baseline to <Week 14: Day of first study medication administration up to and including the day before Week 14 study medication administration
- Week 14 to <Week 26 visit
- Week 26 to <Week 38 visit
- Week 38 to <Week 52 visit
- Safety Period: Week 52 visit to end of study

Safety period includes Week 52 and all later visits. All other periods start with (and include) Baseline visit or Week 14/26/38 visit and end with the day before the next period starts. Start of a new period is always the day of study medication administration. Safety Period starts with the Week 52 Visit. If the Week 52 visit is missing, Safety Period starts 14 days after the last study drug administration of the previous period.

If the Week 14/26/38 visit is missing, the day of the next non-missing visit will be the first day of the new period. For example, if the Week 14 visit was missed but the Week 16 visit was

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conducted, the first time period will end the day prior to the Week 16 visit, This ensures that all Adverse Events (AEs) reported during the initial treatment period are attributed to the initial dose. If no end date for a period can be identified with the above rules, then the period ends 13 days after the last day of study drug administration of that period.

Continuous data will be summarised in terms of the mean, SD, median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarised in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

If not stated otherwise percentages will be presented with one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. 100% will be presented without decimal places.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals (CI) will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.2 or a later version in a secure and validated environment. Tables, listings and figures will each be provided in a separate rtf document as well as in a separate pdf documents.

4.3   Analysis Populations

Screened Population: The SP will consist of all subjects who got screened.

Randomised Population (RP): The RP will consist of all subjects who were randomised to treatment.

Intent-to-Treat (ITT) Population: The ITT population will consist of all subjects who were randomised to treatment and who received at least one dose of study treatment (GSK3196165 or placebo).

Pharmacokinetic (PK) Population: The PK population will consist of all subjects in the ITT population, who had at least one valid pharmacokinetic assessment.

Immunogenicity Population: The immunogenicity population will consist of all subjects in the ITT population, who had at least one valid immunogenicity assessment.

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Actigraphy Population (AP): The AP will consist of all subjects in the ITT population who consent to participate in the actigraphy substudy.

Genetic Research Population (GRP): The GRP will consist of all subjects in the ITT population who consent to participate in the genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

All endpoints will be analysed for the ITT population by randomised treatment group. Numbers and percentages of subjects in each analysis population will be summarised by randomised treatment group. Subjects who received at least one wrong dose will be presented in a listing. Additional summaries may be provided if considered necessary.

A by-subject listing of analysis population details will be provided. This listing will be presented by randomised treatment group and will include: center, subject identifier, inclusion/exclusion flag for each population and reason for exclusion from each population. All subjects screened will appear on this listing.

4.3.1   Analysis Datasets

For each of the efficacy evaluations of binary endpoints, subjects with missing efficacy data, early withdrawals, subjects who received more than 10 mg/day of prednisone equivalent oral corticosteroids, subjects with any new use of parenteral corticosteroids, more than one intra-articular corticosteroid injection within a 24 week period, or subjects who received rescue treatment will be imputed as non-responders and therefore treated as a failure (e.g. no DAS28(CRP) remission or no moderate/good EULAR response). Imputation rules for each case are described in section 4.5.2:

A dataset will be created with these imputation rules and will be referred to as the NRI dataset. The NRI dataset will be the primary dataset used for all binary efficacy endpoints. Imputed response for each binary endpoint will be presented by visit and subject in listings.

For the efficacy evaluations of continuous endpoints, results recorded for subjects who received rescue treatment or exceeded 10 mg/day prednisone equivalent oral corticosteroids, subjects with any new use of parenteral corticosteroids, more than one intra-articular corticosteroid injection within a 24 week period, or subjects who received rescue treatment will be set to missing at the same visits that were set to non-responder for the binary endpoints. This is a change from protocol section 9.3.2. A dataset will be created and will be referred to as the Set-to-Missing (STM) dataset.

For safety endpoints, no imputation for missing data will be done.

4.4   Study Subjects

4.4.1   Disposition of Subjects
A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

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The following subject disposition summaries will be provided: See Section 4.3 for a description of the analysis populations.

A summary of the number of subjects who were screened for entry into the study and
- were excluded prior to randomisation by major reason and overall (Analysis population: All Subjects Screened)
- were randomised per center, per country, and by disease duration (<2 years, ≥2 years) and randomised treatment group (Analysis population: Randomised Population)
- received at least one dose of study medication by randomised treatment group (Analysis population: Randomised Population)
- withdrew from the study by major reason by randomised treatment group (Analysis population: ITT Population)
- completed the study by randomised treatment group (Analysis population: ITT Population)
- completed 12/24/36/50 weeks of treatment by randomised treatment group (Analysis population: ITT Population)
- completed 12/24/36/50 weeks of treatment without dose escalation by randomised treatment group (Analysis population: ITT Population)
- were escalated to highest dose at Week 14/26 by randomised treatment group (Analysis population: ITT Population)
- were escalated to highest dose at Week 14/26 and completed 24/36/52 weeks of treatment by randomised treatment group (Analysis population: ITT Population)
- were withdrawn from study at Week 38 due to lack of EULAR good/moderate response by randomised treatment group (Analysis population: ITT Population)

By-subject listings of eligibility details, randomisation details by site (including subject id, randomisation number and randomised treatment group and information whether the blind was broken at discontinuation), visit dates (including actual treatment received at each visit) and withdrawal/study completion details (including reason for discontinuation and duration of treatment prior to discontinuation) will be provided.

4.4.2   Protocol Deviations

Protocol deviations (PDs) will be managed and reported according to PAREXEL Standard Operating Procedures (SOPs).

Details will be given in the Protocol Deviation Specification (PDS) document, which will include detailed information regarding definitions, classifications, tracking and management of PDs.

PDs will be categorised as major or minor as further described in the PDS.

PDs will also be classified into the following categories: Informed Consent, Inclusion/Exclusion Criteria, Withdrawal Criteria, IP Admin/Study Treat, Disallowed Medications, AE/SAE, Visit Schedule, Procedures/Tests, Other.

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Observable PDs that can only be identified by project team members during the monitoring, but cannot be programmed, will be tracked and reconciled with programmable (data driven) PDs, that can be programmed from the recorded data.

A combined PD dataset will include all PDs.

Special considerations are needed for (potentially) unblinding PDs, which will be handled in separate unblinded areas with restricted access.

Summaries of the number and percentage of subjects with a major/minor protocol deviation will be provided by randomised treatment group and by type of deviation (Analysis population: Randomised Population).

A by-subject listing of all protocol deviations will be provided.

4.5   General Data Handling Conventions

4.5.1   Missing Dates

In analysis of AEs and medication a complete date will be established in order to identify AEs or medication as occurring during treatment or not. For handling partially reported onset/start and outcome/end dates for AEs or medication the following algorithms are applied:

- AEs:

  - Missing onset day, but month and year present:
    If study medication had been taken in the same month and year as the occurrence of the AE, then the onset day of the event is assigned to the day of first dose of study medication.
    Otherwise the onset day is set to the first day of the month (eg, XX-Sep-2010 is considered as 01-Sep-2010).
  - Missing onset day and month, but year present:
    If study medication had been taken in the same year as the occurrence of the AE, then the onset date of the event is assigned to the date of first dose of study medication.
    Otherwise the onset day and month is set to 01 January (eg, XX-XXX-2010 is considered as 01-Jan-2010).
  - Missing outcome day, but month and year present:
    The day is set to the last day of the month (eg, XX-Sep-2010 is considered as 30-Sep-2010).
  - Missing outcome day and month, but year present:
    The outcome day and month is set to 31 December (eg, XX-XXX-2010 is considered as 31-Dec-2010).

- Medications:

  - Missing start day, but month and year present:
    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

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to the day of first study medication administration. 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:
  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.
- 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:
  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:
  The stop day and month is set to 31 December (eg, XX-XXX-2010 is considered as 31-Dec-2010).

- RA diagnosis and symptom onset:

  - Missing day, but month and year present:
    Date is set to the first day of the month (eg, XX-Sep-2010 is considered as 01-Sep-2010).
  - Missing day and month, but year present:
    Date is set to 01 January (eg, XX-XXX-2010 is considered as 01-Jan-2010)

- End date of Tobacco use:
  - Missing outcome day, but month and year present:
    The day is set to the last day of the month (eg, XX-Sep-2010 is considered as 30-Sep-2010).
  - Missing outcome day and month, but year present:
    The outcome day and month is set to 31 December (eg, XX-XXX-2010 is considered as 31-Dec-2010).

In data listings, onset/start and outcome/stop date of AEs, medication, diagnosis, or symptoms is displayed as reported.

4.5.2   Missing Data for Efficacy and Safety Endpoints

4.5.2.1   Missing Data for Efficacy Endpoints

Missing visit data for each efficacy endpoint will be handled as described in Sections 3.2 and 4.3.1. For each continuous endpoint, change from baseline will be missing at visits with missing post-baseline values or where data were imputed to missing.

For the binary endpoints, subjects with missing efficacy data, early withdrawals, subjects who exceed the allowed dose of corticosteroid, who received new parenteral corticosteroids or more than one intra-articular corticosteroid injection within a 24 week period, or subjects who received rescue treatment will be imputed as non-responders and therefore treated as a failure (e.g. no DAS28(CRP) remission or no moderate/good EULAR response).

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For subjects who exceed the allowed dose of corticosteroid, who received new parenteral corticosteroids or more than one intra-articular corticosteroid injection within 24 weeks or subjects who received rescue treatment, continuous efficacy endpoints will be set to missing.

- Missing efficacy data: visits with missing data (due to a missed visit or missing component of a composite endpoint) should be set to treatment failure.
- Early withdrawals (including subjects that are withdrawn at Week 36 due to lack of EULAR response): only visits following the early withdrawal visit should be set to treatment failure.
- Prednisone equivalent >10 mg/day: the visit after a period (time from previous visit up to the day before the current visit) of average daily corticosteroid use exceeding 10 mg/day prednisone and all following visits should be set to treatment failure (continuous endpoints will be set to missing).
- Parenteral corticosteroids: all visits after a subject received any new parenteral corticosteroids (e.g. intravenous and intra-muscular) should be set to treatment failure (continuous endpoints will be set to missing).
- Intra-articular corticosteroids: all visits after the second intra-articular corticosteroid injection within a 24 week period should be set to treatment failure (continuous endpoints will be set to missing).
- Rescue: subjects who rescue to 180 mg dose at Week 14 or 26 should be set to treatment failure at that visit and all subsequent visits (continuous endpoints will be set to missing).

4.5.2.2   Missing Data at Baseline for Efficacy and Safety Endpoints

For efficacy endpoints (including CRP and ESR), a missing value at baseline will not be imputed with the screening results for change from baseline or percent change from baseline calculations; the endpoint will be missing for all visits.

For safety endpoints, a missing value at baseline will be imputed using the prior result that is closest in proximity to baseline in order to calculate change from baseline or percent change from baseline.

4.5.2.3   Multiple Imputation: Predictive Mean Matching

For further sensitivity analyses for DAS28(CRP), multiple imputation may be conducted (see section 4.9.2). If needed, this will be conducted as an ad-hoc analysis by GSK.

The multiple imputation procedure will assume that the observed visit data are from a multivariate normal distribution and that data are missing at random. Depending on the missing data pattern, either the predicted mean matching method (monotone missing pattern) or the MCMC method (either monotone or non-monotone missing pattern) for imputation will be used.

The sensitivity analysis will follow steps 1 to 3:

1.   Using PROC MI, missing data will be filled in *m* times to generate *m* complete datasets using the observed data. If the MCMC method is used, specify IMPUTE=FULL to impute all missing values.

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2.   Change from baseline will be calculated in each of the *m* complete datasets and then analyzed using the appropriate dose response model identified at the second interim analysis.

3.   Using PROC MIANALYZE, the *m* sets of estimated parameters from the dose response model will be combined to form the mean and standard deviation of each parameter for use in inference regarding the dose response relationship at Weeks 24 or 52 visits.

4.5.3   Multiple Assessments and Early Withdrawal Visits

If a variable has been assessed multiple times at the same visit, only the last assessment will be used except for Electrocardiograms (ECGs) or laboratory measurements. Triplicate ECG measures will be averaged for each subject and visit prior to generating summary tables.

For laboratory values the value with the worst CTCAE grade will be considered. If there is more than one value of this grade, the later value will be considered.

Only scheduled visits will be included in summaries. Listings will include scheduled and unscheduled visits.

Early Withdrawal (EW) visits will be assigned to the respective visit according to the Time and Events table in Section 7.1 of the protocol using the day of the EW visit relative to Day 1. For the first 4 weeks an EW visit more than ±3 days in comparison to the target visit will be assigned to the closest target visit. Starting with Week 4, an EW visit more than 7 days after a target visit day will be assigned to the next visit.
If a scheduled visit and an EW visit occur within the same visit window and are both available, the later visit will be used for analyses. The earlier visit will appear in listing only. For efficacy analyses, if an EW visit is assigned to a non-standard efficacy visit, i.e., a visit at which efficacy assessments are not scheduled per the Time and Events Table, then these EW data will be ignored in the statistical analysis.

4.5.4   Oral Corticosteroid Conversion
To assess corticosteroid use and determine average daily corticosteroid dose, all corticosteroid dosages will be converted to a prednisone equivalent in milligrams by multiplying the dose of the steroid (using the coded term from GSKDrug) by the conversion factor to get prednisone equivalent units. Summaries refer to average daily prednisone dose instead of average daily corticosteroid dose. See Table 3 for conversion factors.

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Table 3 Corticosteroid Conversion Factors

Conversion	Steroid
8.333	BETAMETHASONE
8.333	BETROSPAM
0.2	CORTISONE
8.333	CRONOLEVEL
0.83333	DEFLAZACORT
6.667	DEXAMETHASONE
0.25	HYDROCORTISONE
1.25	MEPREDNISONE
1.25	METHYLPREDNISOLONE
2.5	PARAMETHASONE
1	PREDNISOLONE
1	PREDNISONE
1.25	TRIAMCINOLONE

For each scheduled visit, the average daily prednisone dose will be calculated by summing all oral corticosteroid doses (converted to prednisone) 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).

4.6   Demographic and Other Baseline Characteristics

The following Baseline characteristics will be summarised based on the ITT population by randomised treatment group.

Demographic Characteristics
Continuous variables: age (years), height (cm), weight (kg), BMI-Body Mass Index (kg/m²).

Categorical variables: age (18- <65 years and ≥65 years), sex (male, female), child bearing potential (for females: yes, no), ethnicity (Hispanic or Latino, Not Hispanic or Latino), race (African American/African Heritage, American Indian or Alaskan Native, Asian – Central/South Asian Heritage, Asian – East Asian Heritage, Asian – Japanese Heritage, Asian – South East Asian Heritage, Native Hawaiian or Other Pacific Islander, White – Arabic/North African Heritage, White/Caucasian/European Heritage) and BMI (<18.5, 18.5 - <25, 25 - <30, ≥30).

An additional summary will include age, sex and race for placebo group and combined GSK3196165 treatment groups.

Baseline efficacy parameters
Continuous baseline efficacy parameters and components will be summarised in a separate table.

Medical history

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Prior and concomitant medical history will be summarised by reported term. Cardiac disorders will be shown separately.

Disease history
RA disease history will be summarised in form of disease duration (duration from formal RA diagnosis to first study medication administration) categorical (< 2 years/ ≥ 2 years) and as summary statistics (in months), RA functional class and time since start of RA symptoms (in months).

Separate by-subject listings of demographic data and other baseline characteristics, prior and concomitant medication, medical history, RA medication use and disease history will be provided.

4.7   Medication Use

Prior and concomitant medication use
Prior and concomitant medications will be summarised by Anatomical Therapeutic Chemical (ATC) classification and randomised treatment group in separate tables. Medications that are both prior and concomitant will appear in both tables.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, imputations are done as described in section 4.5.1 and the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through partial dates as described in section 4.5.1) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Prior and concomitant corticosteroid use will be shown in a separate listing.

RA medication use
Prior and concomitant RA medication will be summarised by ATC classification and randomised treatment group.

Oral Corticosteroid use

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Change from baseline in average daily prednisone dose will be summarised by visit. The number and percentage of subjects with ≥25% decrease from baseline and to below ≤7.5 mg/day will be summarised at Weeks 12, 24, 36, 48 and 52.

4.8 Treatment Compliance

Summaries will be based on the ITT population and will be provided by randomised treatment group and time period.

Study Treatment
Treatment compliance for GSK3196165 will utilize the administered volume and compare it to the scheduled expected volume. The general formula for the compliance ratio (CR) is given as follows:

$$CR = \frac{\text{actual volume (mL)} * 100}{\text{expected volume (mL)}}\%$$

The expected volume is based on the planned number of doses (based on each subjects time in the study) and study treatment volumes provided in the protocol Section 6.1. If a subject completed the study without escalation, then the total number of doses would be 28 and the total expected volume for each treatment group would be as follows: placebo=16.8mL; 22.5mg=4.2mL; 45mg=8.4mL; 90mg=16.8mL; 135mg=25.2mL; 180mg=33.6mL. The actual volume is the sum of the volume of doses received in mL. If a subject escalates to 180mg dose, the 180mg volume times the number of doses would be included in the expected volume. The ratio will be summarised as a continuous variable as well as categorically (<80% and ≥80%) and will be shown separately for administrations of randomised treatment and administrations after escalation.

Additionally, number and percentage of subjects who missed at least two doses of GSK3196165 will be summarised by period.

Methotrexate
Numbers and percentages of subjects who increased or decreased their MTX dose or missed a MTX dose during the conduct of the study will be shown separately for administrations before escalation and after escalation.

A by-subject by-period listing of treatment compliance ratio for GSK3196165 will be provided.

4.9 Efficacy Evaluation

4.9.1 Statistical Considerations

4.9.1.1 Hypotheses for Primary Endpoint and Dose-Response Relationship

Primary endpoint (remission at Week 24):

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The study will test the null hypothesis that there is no difference between any dose of GSK3196165 and placebo in the proportion of subjects with remission (DAS28(CRP)<2.6) at Week 24 versus the alternative hypothesis that at least one of the GSK3196165 dose groups differs from placebo in the proportion of subjects with remission at Week 24.

> H0: No difference between placebo and the 5 active doses

> H1: At least one of the 5 active doses differs from placebo

Dose response relationship (change from baseline in DAS28(CRP) at Week 12):

The null hypothesis (H0) for the dose response relationship assumes that there is no effect of the test drug and hence no evidence of a dose response relationship with respect to the change from baseline in the DAS28(CRP) continuous score. This is equivalent to saying that none of the active doses differs from placebo:

> H0: Placebo = 22.5 mg = 45 mg = 90 mg = 135 mg = 180 mg

Whereas the alternate hypothesis (H1) assumes that there is a significant relationship between GSK3196165 dose and response with respect to the change from baseline in the DAS28(CRP) continuous score. It is expected that this relationship will follow an Emax model or more generally is a monotone relationship:

> H1: Placebo $\geq$22.5 mg $\geq$45 mg $\geq$90 mg $\geq$135 mg $\geq$180 mg

4.9.1.2 Multi-center Studies

This study will randomise 210 subjects into 6 treatment arms, so that on average only 35 subjects per arm will be enrolled (although some arms may have larger patient numbers if inferior arms are dropped at the interim analyses). The number of sites (centres) may be roughly around 70, so that an adjustment of the analyses by centre will not be feasible.

For all analyses all sites, countries and regions will be pooled.

4.9.1.3 Adjustments for Covariates

Adjustment for the following covariates will be considered: baseline value, disease duration (<2 years, >=2 years), weight, age, and sex.

4.9.1.4 Multiple Comparisons/Multiplicity

For this phase II study no adjustment for multiple testing is planned.

4.9.1.5 Interim and Final Analyses

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Two interim analyses, one primary endpoint analysis and a final analysis are planned during the course of this study. Unblinded results will be presented to the DRC where the decision to drop treatment arms or stop the study based on benefit/risk relationship or based on safety findings alone will be made as detailed in the DRC Charter or DRC Statistical Guidance document. See section 4.10.11 for additional DRC information.

The timing and content of each deliverable is summarised in the following table.

Table 4 Interim and Final Deliveries

Analysis	Timing	Deliverable	Unblinded Team	Main Objective
Interim 1	90 subjects complete Week 4	**PAREXEL**: ADAM datasets and demography table (see Table 5) **GSK**: efficacy displays (see Table 5) and PK if required	Unblinded PAREXEL programmers, GSK lead and QC statistician, DRC	Evaluate whether to stop the study based on: • Dose response relationship at Week 4 (i.e., if all doses have > -0.4 point difference over placebo using the Week 4 dose response model estimates for change from baseline in DAS28(CRP)).
Interim 2	90 subjects complete Week 12	**PAREXEL**: ADAM datasets and demography table (see Table 5) **GSK**: efficacy displays (see Table 5) and PK if required	Unblinded PAREXEL programmers, GSK lead and QC statistician, DRC	Evaluate whether to stop the study based on: • Dose response relationship at Week 12 (i.e., if **all** doses have > -1.0 point difference over placebo using the Week 12 dose response model estimates for the change from baseline in DAS28(CRP)). • Dose response relationship and predictive probabilities (i.e., if **at least one** dose ≤ -1.0 over placebo using the Week 12 dose response model estimates but the predictive probabilities of seeing a 25% difference at Week 24 in DAS28(CRP) remission is <30%). Evaluate whether to drop a treatment arm based on: • An individual dose with > -1.0 point difference over placebo using the Week 12 dose response model estimates for change from

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				baseline in DAS28(CRP).
Week 24	All subjects complete Week 24 visit	**PAREXEL**: Unblinded Week 24 displays.	PAREXEL lead and QC biostatisticians and programmers, GSK.	Unblinded primary/ secondary analyses, safety and PK.
Final	All subjects complete the study (follow-up visit at Week 62)	**PAREXEL**: All unblinded displays, including exploratory endpoints, SDTM and ADAM datasets.	PAREXEL lead and QC biostatisticians and programmers, GSK.	Final reporting for Study 201755.

Unblinded interim analyses will be conducted when 90 subjects (i.e. on average 15 per arm) have completed 4 and 12 weeks of treatment. Efficacy analysis for the interim analyses will not be analysed by PAREXEL but by GSK. These interim analyses will be aligned with the unblinded safety review of the DRC where possible, see section 4.10.11.

4.9.1.6   Examination of Subgroups

A subgroup analysis for subjects with early RA (i.e. < 2 years disease duration before first study medication administration) will be conducted if there are at least 10% subjects with early RA in the ITT population.
Additionally, subgroup analyses for selected endpoints may be conducted by gender if an adequate number of subjects are represented in each subgroup.

The following endpoints will be summarised for all subgroups in the same way as done for the entire population:

- DAS28(CRP) remission at all assessment points
- Change from Baseline in DAS28(CRP) at all assessment points
- ACR 20/50/70 response rates at all assessment time points

The following outputs for key safety endpoints will be provided by randomised treatment group for all subgroups:

- Overall summary of AEs
- Number and percentage of subjects reporting an AE by SOC and PT
- Number and percentage of subjects reporting a serious AE by SOC and PT
- Summary of AESIs
- Summary of subjects with pulmonary findings

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4.9.2   Key Efficacy Analyses

4.9.2.1   Interim Analyses

The outputs listed in Table 5 will be produced at the efficacy interims. All data will be summarised using the Intent-to-Treat population.

The second interim analysis may allow an assessment of subjects with early RA (<2 years disease duration). Results may impact the proportion of subjects randomised to this subgroup.

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Table 5 List of Outputs for Interim Analyses (IA)

Endpoint	Output	IA1	IA2	Produced by
n/a	Summary of Demography Characteristics – Disease History	Y	Y	PAREXEL[1]
DAS28(CRP) change from baseline	Summary of the Change from Baseline in DAS28(CRP) at Each Visit	Y	Y	GSK
	Plot of Mean and 95% CI of Change from Baseline in DAS28(CRP) by Visit and Randomised Treatment Group (1 plot)	Y	Y	GSK
	Plot of Mean and 95% CI of Change from Baseline in DAS28(CRP) Across Doses at Weeks 4, 8 and 12 (3 plots)	Y	Y	GSK
	Mixed Model Repeated Measures Analysis (MMRM) of Change from Baseline in DAS28(CRP) Through Week 12	Y	Y	GSK
	Plot of Least Squares Means and 95% CI of Change from Baseline in DAS28(CRP) (from MMRM)	Y	Y	GSK
	Dose Response Modelling of Change from Baseline in DAS28(CRP) at Weeks 4, 8 and 12	Y	Y	GSK
	Plot of Dose Response Model at Weeks 4, 8 and 12	Y	Y	GSK
	Posterior Probability of the Difference in the Change from Baseline over Placebo < -1.0 at Week 12 for Each Dose	Y	N	GSK
DAS28(CRP) remission	Proportion of Subjects in DAS28(CRP) Remission at Week 24	N	Y	GSK
	Predictive Probability of the Difference Over Placebo in the Proportion of Subjects in DAS28(CRP) Remission at Week 24 being > 25%	N	Y	GSK
ACR response	Proportion of Subjects with an ACR20/50/70 Response at Each Visit	Y	Y	GSK
[1] Produced by the unblinded programming team.				

DAS28(CRP) change from baseline

DAS28(CRP) scores and changes from baseline will be summarised for each visit. The mean change from baseline in DAS28(CRP) score and 95% CI will be plotted by randomised treatment group.

For change from baseline in DAS28(CRP) score, a mixed model repeated measures (MMRM) analysis will be conducted including all weeks up through Week 12. For the first interim the analysis will subset on those subjects with Week 12 DAS28(CRP) scores. The model will be fitted with fixed effects for randomised treatment group, visit, treatment by visit interaction and baseline DAS28(CRP), and visit within subject as a repeated effect. The covariance will initially be specified as unstructured covariance matrix. If SAS® gives a non-convergence warning, the

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results will not be used – instead the warning will be stored and the spatial power law structure will be used in order to reduce the number of parameters to be estimated.

The point estimates and corresponding 95% CI for the treatment differences will be constructed using the residual error from the model; these estimates will be summarised and plotted for each randomised treatment group comparison over time.

Dose-Response at Weeks 4, 8 and 12

A plot of the mean change from baseline in DAS28(CRP) score and 95% CI versus dose will be provided separately for each of Weeks 4, 8 and 12.

The dose-response relationship for the change from baseline in DAS28(CRP) score will be evaluated at Week 4, 8 and 12 using a three parameter E_{max} model of the form:

$$Y = E_0 + E_{max} * [D_i / \{ ED_{50} + D_i \}]$$

where E_0 is the placebo effect, E_{max} is the maximum achievable effect above placebo, ED_{50} is the dose at half E_{max} and D_i are doses $= 0, 22.5, 45, 90, 135$ and 180 mg. Y is a measure of change from baseline in DAS28(CRP) continuous score.

If this Emax model is not applicable then additional models will be investigated, including a four parameter E_{max} model with a slope factor $B > 0$:

$$Y = E_0 + E_{max} * [D_i^B / \{ ED_{50}^B + D_i^B \}]$$

and the model with the expected response as a linear function of dose:

$$Y = E_0 + E_1 * D_i$$

Each of the models will be fitted to the data and their fit compared using the Akaike information criteria (AIC), where the model with the lowest AIC will be the primary model for inference. The additional models will be considered secondary models, and will not be utilised unless issues arise with the residual checks on the primary model. Distributional assumptions will be assessed by examining plots of the residuals from the primary model.

The final model parameters for the dose-response will be summarised; a plot of the dose-response relationship will be provided. The chosen models might differ between Week 4, 8 and 12. SAS outputs of all secondary models will be shown.

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Posterior Probabilities at Week 12

In addition to assessing the dose response model for the DAS28(CRP) change from baseline data at Weeks 4, 8 and 12, the posterior distribution for the Week 12 change from baseline in DAS28(CRP) will be calculated.

This will be derived assuming the data follow a normal distribution with mean μ_i and precision τ_i (where i=0 is the placebo group and i=1-5 are the treatment groups) and non-informative prior distributions for μ and τ:

$$\mu_i \sim N(0, 10^{-2})$$

$$\tau_i \sim Ga(0.001, 0.001)$$

Given the small number of subjects expected with Week 12 data at the first interim analyses, alternative prior distributions for τ may be investigated.

Markov-Chain-Monte-Carlo (MCMC) methods in SAS® will be used to derive the posterior distributions for each randomised treatment group and to also derive the distribution of the difference between each treatment group and the placebo group. From this difference distribution the posterior probability that the treatment difference between each active dose and placebo being > 1 will be calculated.

Decision criteria for stopping the study after Interim Analysis 1 are specified in the DRC Statistical Guidance Document.

DAS28 (CRP) remission rates at Week 24

The number and percentage of subjects achieving DAS28(CRP) remission (DAS28(CRP) < 2.6) will be summarised for each randomised treatment group and visit. Fisher's exact test will be used to test for randomised treatment group differences at Week 24 in the proportion of subjects achieving remission for each GSK3196165 treatment group versus placebo.

Predictive Probabilities at Week 24

The proportion of subjects with available DAS28(CRP) remission data at week 24 at the interim analysis will only be summarised using counts and proportions. This is because only a low number of subjects with week 24 data are expected at the week 12 interim analysis.

In addition, the predictive probability that the difference in DAS28(CRP) remission between each dose and placebo at the end of the study is > 15% and > 25%, given the results at the interim analysis and the prior information will be calculated using the procedure described below.

The following information will be available at the interim:

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- l_i = number of subjects that have reached week 24 in each randomised treatment group i, i=0,...,5 (i=0 being the placebo arm and i=1-5 being the 5 treatment groups, with i=1 being 22.5mg)
- x_i = observed number of subjects in DAS28 remission at week 24 in each randomised treatment group i, i=0,...,5 (i=0 being the placebo arm and i=1-5 being the 5 treatment groups, with i=1 being 22.5mg)

Our prior Beta distribution on the remission rate in each randomised treatment group: $\pi_i \sim \text{Beta}(\alpha^0_i, \beta^0_i)$

- Placebo: $\alpha^0_0 = 9$, $\beta^0_0 = 91$, so the prior mean remission rate is 9%, and the 95th interval is (4%, 15%)
- Active group: $\alpha^0_i = 1$, $\beta^0_i = 1$, equivalent to a uniform distribution (non informative). This will apply to all active groups (i=1 to 5)

The algorithm is as follows:
1. Compute the interim posterior distribution of the remission rate π_i in each randomised treatment group:
$$\pi_i \sim \text{Beta}(\alpha_i = \alpha^0_i + x_i, \beta_i = \beta^0_i + l_i - x_i)$$

2. For each of the 6 treatment groups, a sample of the number of subjects with DAS28 remission post-interim is generated from the following predictive distribution (Beta-Binomial):
$$y_i \sim \text{beta-Binomial}(\text{sample}= m_i - l_i, \alpha_i, \beta_i)$$
Where $m_i - l_i$ is the number of subjects remaining post-interim, α_i and β_i are the parameters of the interim posterior distribution of the remission rate as calculated in (1).

10,000 replicates will be used per treatment group.

3. For each replicate, compute the distribution of the remission rate in each treatment group:
$$\pi_j \sim \text{Beta}(\alpha_i + y_i, \beta_i + m_i - y_i)$$
and therefore generate a sample of 10,000 simulations.

For each treatment group, we will obtain a matrix with 10000x10000, each column corresponding to the predictive distribution of π_i for each replicate from (2).

4. Calculate the posterior predictive distribution of the difference $\pi_i - \pi_0$, for i = 1,...,5
For each of the 5 differences, we obtain again a matrix with 10000x10000, each column corresponding to the predictive distribution of the difference for each replicate from (2).

5. The posterior predictive probability $p_j = P(15\% < \pi_j - \pi_0 < 25\%)$, j=1,...,5, is calculated empirically by counting how many times the rule is met in the sample of the difference for each replicate. The median is used over the 10,000 replicates.

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For sensitivity analysis purposes, other prior distributions for the placebo arm may be assessed based on emerging data on this endpoint, including assuming a non-informative prior.

The predictive probabilities to have an improvement of 25 percentage points over placebo will be used for the decision making, i.e. potentially dropping treatment arms or stop the study for futility. Decision criteria are specified in the DRC Statistical Guidance Document.

ACR20/50/70 response rates at all assessment points

The number and proportion of ACR20, ACR50 and ACR70 responders will be summarised for each randomised treatment group and visit. Fisher's exact test will be used to test for randomised treatment group differences in the proportion of ACR20/50/70 responders at all assessment points for each GSK3196165 treatment group versus placebo.

4.9.2.2   Week 24 Analysis and Final Analysis

The goal of the Week 24 analysis is to provide unblinded results for all endpoints that are evaluable at this timepoint except actigraphy. The Final analysis will include all analyses and endpoints.

For the Week 24 analysis, tabular summaries of efficacy data will be provided at all visits through Week 62 where available. Graphical presentations for efficacy endpoints will include data through the Week 24 visit. Statistical analyses will also include data through the Week 24 visit. All safety data collected at the time of the Week 24 data cut will be summarised. See section 4.9 for a description of safety summaries.

The following table indicates the types of summaries and analyses that will be conducted for each primary and secondary efficacy endpoint.

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Table 6 Summaries and Analyses for Primary and Secondary Endpoints

	Summary Statistics					Statistical Analyses								
	Observed	CfB/Proportion			Subgroups	Dose Response			MMRM/Logistic			Survival (Time to 1st)		
	T	T	F	L	T	T	F	O	T	F	O	T	F	O
DAS28(CRP) score	Y	Y	Y	Y	Y1	Y at Week 24	Y	Y	Y	Y	Y			
DAS28(CRP) remission		Y		Y	Y1	Optional at Week 24	Y	Y	Y		Y	Y	Y	Y
DAS28(CRP) EULAR response		Y		Y	Y1				Y		Y			
ACR20/50/70		Y		Y	Y1				Y		Y			
Components: TJC28, TJC68, SJC28, SJC66, CRP, PtGA, PhGA	Y	Y		Y					Y		Y			
Index- and Boolean-based ACR/EULAR remission		Y			Y1				Y		Y			
CDAI remission		Y							Y		Y			
SDAI, CDAI scores	Y	Y							Y	Y	Y			
HAQ-DI score	Y	Y							Y	Y	Y			
HAQ-DI pain severity				Y										
Pain score	Y	Y							Y	Y	Y			
SF-36 physical, mental and domain scores	Y	Y							Y	Y	Y			
FACIT-Fatigue	Y	Y		Y					Y	Y	Y			
BFI Question 3	Y	Y		Y					Y	Y	Y			
CfB=Change from baseline; T=table; F=figure; L=listing; O=supportive analysis SAS output. 1 Disease duration ((<2 years, ≥2 years), gender.														

For plots of change from baseline endpoints, the mean change from baseline and 95% CI will be plotted by randomised treatment group.

Plots of Mean and 95% CI of Change from Baseline in DAS28(CRP) at Each Visit will be created.
Subject profile plots of DAS28 score at each visit will be produced.

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Dose response analyses for change from baseline in DAS28(CRP) will be conducted after visual inspection of the mean and 95% CI plots and using the final model from the second interim analysis as a starting point for the dose response modelling. The Week 24 primary analysis model will be fitted without covariate terms. A plot of the residuals versus predicted values will be examined to assess distributional assumptions. If additional models are fit, the smallest AIC will be used to help identify the best fitting model. Covariates from the Week 24 primary analysis of DAS28(CRP) remission may be added to the model in a sensitivity analysis. Model results from the sensitivity analysis will be provided in the corresponding listing.

Dose response analyses for DAS28(CRP) remission might be done as an ad-hoc analysis. MMRM analyses will be conducted similarly to interim analysis methods. Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the predicted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. If there are any departures from the distributional assumptions, alternative models may be explored using appropriate transformed data

For change from baseline in DAS28(CRP), if the dropout rate is ≥10% for the Week 24 or Week 52 analysis, further sensitivity analyses using multiple imputation as explained in section 4.5.2.3 may be conducted as ad-hoc analyses. In order to assess subgroup effects, additional analyses will be conducted with subgroup and subgroup interaction with treatment as covariates.

For DAS28(CRP) remission, subjects with missing data as defined in Section 3.2.1 will be imputed as non-responders as described in Section4.5.2.1. Differences in remission rates between each active arm and placebo will be summarised at each visit through Week 52. 95% CI for the differences will be constructed using their asymptotic standard errors (asymptotic Wald confidence limits) without continuity correction.

Logistic regression models will have fixed effects for randomised treatment group and baseline value. The odds ratios, 95% CI and p-values for the comparison of each GSK3196165 treatment group versus placebo at key time points will be presented. Covariates age, gender, weight and disease duration (<2 years, ≥2 years) will be considered in alignment with the results of the primary analysis model.

For ACR response, baseline values of TJC68 and SJC66 will be considered as fixed effects, as a baseline value of ACR response does not exist.

For binary endpoints with repeated measures over time, Generalized Estimating Equations (GEE) methodology will be used to take correlation among subject-level responses over time into account. The model will include data from all assessment points from Week 1 to Week 62. Due to only few expected subjects with remission in some randomised treatment groups (especially placebo) only standard errors and resulting confidence intervals will be adjusted. To this end an independent working correlation structure will be assumed and standard errors will be calculated based on the empirical sandwich covariance estimate (default setting for PROC GENMOD in SAS) (Stokes, Davis, & Koch, 2012).

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For the primary analysis of DAS28(CRP) remission at Week 24, the GEE model will include terms for randomised treatment group, baseline DAS28(CRP), visit and interaction terms for treatment group-by-visit and baseline-by-visit. A sensitivity analysis including covariates age, gender, weight and disease duration (<2 years, ≥2 years) will be considered by adding covariate terms to the repeated measures model one at a time along with the covariate-by-treatment group interaction term. If the interaction term is not significant at $\alpha=0.10$ it will be removed from the model. Likewise, if the covariate term is not significant at $\alpha=0.10$ it will be removed from the model. Other covariates will be tested in a similar manner.

Survival analyses (time to event analyses) will be conducted for the final analysis using Kaplan-Meier methods, comparing each GSK3196165 dose to placebo. Between-group differences will be analysed using the log-rank statistic. Median time to remission will be presented for each randomised treatment group. Kaplan-Meier plots of the time to remission will be presented. Subjects who withdraw from the study are censored at the time of withdrawal. All other subjects are censored at the end of the study.

In addition to summaries of the individual components of composite endpoints, numbers and percentages of subjects meeting the following criteria will be presented:
- TJC68 ≤ 1
- SJC66 ≤ 1
- CRP ≤ 1mg/dl
- PtGA ≤ 10
- SDAI ≤ 3.3

4.9.3   Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will only be analysed at the final analysis.

4.9.3.1   Proportion of subjects achieving sustained (≥24 continuous weeks including the Week 52 visit) DAS28(CRP) remission

Proportion of subjects achieving sustained remission will be analysed and summarised as described in section 4.9.2 for DAS28(CRP) remission, but without using any GEE methods..

The duration of sustained DAS28(CRP) remission will be summarised.

4.9.3.2   Proportion of subjects achieving Major Clinical Response (ACR70 for ≥24 continuous weeks including the Week 52 visit)

Proportion of subjects achieving major clinical response as described in section 3.2.2 will be analysed and summarised in the same way as described in section 4.9.2.2 for DAS28(CRP) remission, but without using any GEE methods.

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4.9.3.3   DAS28(ESR) scores/responses at all assessment timepoints.

DAS28(ESR) scores will be summarised by EULAR response (moderate/good response and no response), observed values, change from Baseline and remission (DAS28(ESR)<2.6) at all assessment points.

4.10   Safety Evaluation

All safety summaries and analyses will be based upon the ITT population by actual treatment group at the time of safety event or assessment. Actual treatment group is either the randomised treatment group or "Rescued Subjects" for subjects who got escalated. Only assessments that happen after the administration of the first dose of rescue treatment will be assigned to the treatment group of "Rescued Subjects".

4.10.1 Extent of Exposure

The extent of exposure to GSK3196165 will be evaluated by summarizing the number of injections, the amount of study medication received in mg and the duration of drug exposure in days. Exposure to GSK3196165 will be summarised by time period (Overall, Day 1 to <Week 14, Week 14 to <Week 26, Week 26 to <Week 38, and Week 38 to <Week 52).
Duration of drug exposure will be calculated as:

- date of the last injection during study – date of first injection during study + 1 day

Weekly MTX dose will be averaged across the entire study and within each time period for each subject.
MTX dose should be documented in mg, but in case ml is captured the following conversion should be used: 1ml is equivalent to 25mg.

A contingency table will be created for Week 12 and Week 24 showing the number of subjects that were escalated/not escalated correctly/falsely. For Week 36 a corresponding table will be created showing correct and false withdrawals due to lack of EULAR good/moderate response.

Overall Extent of exposure and extent of exposure by time period will also be presented in by-subject listings.

4.10.2 Adverse Events

AEs will be coded using the MedDRA in the latest available version.

Treatment emergent AEs (TEAE) are defined as AEs starting on or after the first administration of study medication and up to 12 weeks after last dose of study medication. AEs that are not treatment emergent are defined as pre-treatment AEs or post-treatment AEs, respectively.

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

Table 7 Adverse Events of Special Interest

AESI	Programmatical Derivation

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Serious infections, including serious respiratory infections.	SAEs, Filter on infections SOC
Opportunistic infections including TB reactivation	Opportunistic infections will be adjudicated by the SRT, using the preferred terms list given in Appendix A. Final adjudication conducted by SRT.
Neutropenia	Based on Grade 3 or 4 absolute neutrophil count
PAP (Pulmonary alveolar proteinosis)	If identified then list all AEs for those subjects.
Hypersensitivity reactions, including anaphylaxis	Hypersensitivity reactions will be adjudicated by the SRT, using AE data and data from hypersensitivity reactions eCRF page. Final adjudication conducted by SRT.
Injection site reactions	Using data from Injection site reactions eCRF page

AEs with missing intensity will be considered severe. AEs with missing relationship to study medication will be considered as related both to GSK3196165/Placebo and to MTX.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through partial dates as described in section 4.5) to suggest that the adverse event started prior to the first dose of study treatment or more than 12 weeks after the last dose of study treatment.

Adverse Events will be summarised by system organ class (SOC) and preferred term (PT) Summaries will provide the number of subjects reporting at least one AE and the total number of events reported.

The following summaries of AEs will be provided by actual treatment group at the time of the AE:

- Overall summary of AEs, including number and percentages of subjects with
    - Any AE
    - Serious AE
    - Discontinuation due to AE
    - Drug-related AE
    - AE leading to death
- Overall summary of Adverse Events
- Number and percentage of subjects reporting an Adverse Events
- Most common AEs (reported by >5% of the subjects in total)
- Plot of Most Common Adverse Events and Relative Risk
- Number and percentage of subjects reporting an Adverse Events by maximum intensity
- Number and percentage of subjects reporting an adverse events by relationship to study treatment
- Number and percentage of subjects reporting an adverse events of special interest

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- Number and percentage of subjects that withdraw from study or discontinue study treatment as result of an adverse event
- Number and percentage of subjects with adverse events during the initial treatment period (up to Week 14 visit)
- Number and percentage of subject reporting an adverse event by study period at the time of the first onset of the adverse events
- Exposure-adjusted (patient years) adverse events by treatment group, where the total number of subjects for each column includes all subjects who took the dose at least once during the study. The exposure-adjusted rate divides the total number of AEs attributed to each dose by duration of exposure (in years) to that dose. The duration for subjects who complete the study on their randomised dose is (date of last dose – date of first dose + 1). For subjects who escape, duration is based on treatment periods defined in Section 4.2.

Exposure adjusted incidence rates are calculated as X/T*100 with
- X being the number of occurrences of the relevant AE for subjects while being in the corresponding treatment group
- T being the cumulative duration of exposure (in years) for subjects in the corresponding treatment group

Adverse event summaries will be ordered by decreasing frequency for SOC, and PT within SOC, summed up for all subjects and then alphabetically for SOC, and PT within SOC.

A by-subject listing of all adverse events will be provided as well as a by-subject listing of all AEs leading to withdrawal from study. These listings will be presented by actual treatment group and will include: center, subject identifier, age, sex, race, weight, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, intensity, action taken, outcome, relationship to study medication, action taken with study medication, other action taken and whether the AE is treatment-emergent, serious and an AE of interest.

4.10.3 Deaths and Serious Adverse Events

The following summaries will be provided by actual treatment group at the time of the event:

- Number and percentage of subjects reporting a serious AE by SOC and PT
- Number and percentage of subjects reporting a serious AE by relationship to study treatment
- Number and percentage of AEs leading to death by relationship to study medication
- Exposure-adjusted (patient years) serious adverse events by treatment group, where the total number of subjects for each column includes all subjects who took the dose at least once during the study. The exposure-adjusted rate divides the total number of serious AEs attributed to each dose by duration of exposure (in years) to that dose. The duration for subjects who complete the study on their randomised dose is (date of last dose – date of first dose + 1). For subjects who escape, duration is based on treatment periods defined in Section 4.2.

The following listings will be provided:

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- A by-subject listing of all Serious AEs
- A by-subject listing of all AEs leading to discontinuation of study treatment
- A by-subject listing of all Serious AEs leading to death

4.10.4 Disease-related Events

Disease-related Events (DREs) will be summarised in alphabetical order by actual treatment group at the time of the event. A by-subject listing of all DREs that occurred during the study will also be provided.

4.10.5 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 actual treatment group at the start time of the event.

Event	Definition
Persistent cough	Cough grade 2 or greater recorded for 3 consecutive weeks (15 or more days) on the eCRF page.
Persistent dyspnea	Borg Scale grade 3 or greater recorded for 3 consecutive weeks (15 or more days) on the eCRF page.
Persistent decrease of D_{LCO} by >15%	Relative decrease of DLCOHCPP of $\geq$15% compared to Baseline for 3 consecutive weeks (15 or more days)

These definitions are provided for guidance to identify potential cases. Final adjudication will be conducted by the SRT.

4.10.6 Cardiovascular Events

Occurrences of the below cardiovascular events will be listed in 9 separate listings:

- Arrhythmias
- Congestive heart failure
- Cerebrovascular event stroke and transient ischemic attack
- Deep vein thrombosis/ Pulmonary embolism
- Myocardial Infarction / Unstable Angina
- Peripheral arterial thromboembolism
- Pulmonary Hypertension
- Revascularisation
- Valvulopathy

All relevant data captured in the CRF will be listed. However, as only very few events might occur during the conduct of the study, the design of the listings might be adapted to the actual observed data.

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4.10.7 Liver Events

Liver chemistry stopping events as defined in the protocol trigger further assessments (e.g. liver PK sampling, assessment of alcohol intake, liver biopsy…).

All relevant data captured in the CRF will be listed. However, as only very few events might occur during the conduct of the study, the design of the listings might be adapted to the actual observed data.

4.10.8 Clinical Laboratory Evaluation

Hematology and biochemistry samples will be taken at Screening, Baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 36, 42, 52, at follow-up visit and at a potential early withdrawal visit.

Urinalysis will be taken at Screening, Weeks 4, 8, 12, 16, 20, 24, 32, 42, 52, at follow-up visit and at a potential early withdrawal visit.

The central laboratory will analyse and assess blood and urine samples for the following:

Table 8 Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hemoglobin	Sodium	**Urine dipstick**
Hematocrit	Potassium	Glucose
Mean cell volume (MCV)	Calcium	Protein
Mean corpuscular hemoglobin (MCH)	Phosphate	Creatinine
Mean corpuscular hemoglobin concentration (MCHC)	Urea	
	Creatinine	Microscopy of urine
Erythrocyte mean corpuscular Volume	Creatinine clearance	sediment for
Erythrocyte count	(calculated)	erythrocytes,
Reticulocyte count	Aspartate transaminase (AST)	leukocytes and casts
Leukocyte count	Alanine transaminase (ALT)	if urine dipstick
Leukocyte differential count	γ-glutamyl transpeptidase	abnormal
neutrophils	(GGT)	
eosinophils	Lactate dehydrogenase (LDH)	Urine pregnancy
basophils	Alkaline phosphatase (AP)	test
monocytes	Bilirubin (total)	
lymphocytes	Creatine Phosphokinase (CPK)	
Platelets	Total protein	
Activated partial thromboplastin time (aPTT)	Albumin	
Prothrombin Time (PT)	Albumin/globulin ratio	
International Normalised Ratio (INR)	Serum Glucose	
Fibrinogen	C-reactive protein (CRP)	
Erythrocyte Sedimentation Rate (ESR)*	Cholesterol	
	Triglycerides	
	High-density lipoprotein (HDL)	
	Low-density lipoprotein (LDL)	

*Measured locally

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Descriptive statistics for observed values and change from baseline will be presented by treatment for each visit and for all parameters for hematology, biochemistry and urinalysis, separately. Estradiol, follicle stimulating hormone and rheumatoid factor will be assessed only at Baseline and will be listed.

Laboratory values reported below the limit of quantification (BLQ) will be replaced by one-half the limit of quantification when reporting summary statistics.
Laboratory parameters of interest will be summarised (number and percentages) by time point and by grade as defined in Appendix B.

A summary of shift from baseline to worst grade during the study value will be provided for specific laboratory parameters of interest from Appendix B to be identified in the final version of this analysis plan.

Boxplots will be produced to display the distribution of results for laboratory parameters of interest by time point and by actual treatment group; these parameters are specified in Appendix B.

Separate by-subject listings of laboratory data for hematology, biochemistry and urinalysis will be provided by randomised treatment group, with abnormal values highlighted, and including center, subject identifier, age, sex, race, weight and visit. For each subject, all results for any lab parameter that has at least one abnormal value will be included in the listing. Laboratory reference ranges (Lower Limit of Normal, upper Limit of Normal) will be presented for each laboratory parameter.

4.10.9 Pulmonary assessments

All pulmonary assessment results (chest X-ray, cough, Borg dyspnea questionnaire, chest auscultation, pulmonary function tests (PFTs - spirometry, gas transfer [D_{LCO}]) and pulse oximetry) will be provided in listings.

Summary statistics will be provided for the change from baseline for the Borg dyspnea score, for pulmonary function tests, spirometry and D_{LCO}, and for pulse oximetry by visit. The number and percentages of subjects having a cough for each grade will be summarised by visit, in addition to the number and percentages of subjects having a relative decrease in D_{LCO} Hemoglobin-corrected Percent of Predicted (DLCOHCPP) of >15% from baseline.

A subject's baseline DLCOHCPP value will be taken as the lowest value obtained from the Screening or Day 1 assessment, or any unscheduled visit in between. For rescreened subjects, only the last available Screening assessment will be considered.
The same visit that has been determined to provide the baseline value of DLCOHCPP will be used to provide the baseline value for all other pulmonary function test parameters (including DLCO Absolute Value, HGB corrected DLCO, FEV1, FVC, FEV1/FVC, percent predicted FEV1, percent predicted FVC, predicted FEV1, predicted FVC).

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For summary tables, reporting of subjects with >15% decrease from baseline will be shown separately for subjects with current D_{LCO} <70%. A separate summary will be provided by baseline D_{LCO} value (<70% and ≥70%).

Individual patient profiles of D_{LCO} over time will be shown in a figure by randomised treatment group.

4.10.10 Vital Signs, Physical Findings and Other Observations Related to Safety

The following vital signs will be assessed at screening, baseline, follow-up visit, early withdrawal-visit and several visits in between:

Temperature (in °C), systolic and diastolic blood pressure (mmHg), Heart rate (beats/min), respiration rate (breaths/min), weight(kg) and calculated BMI (kg/m²).

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening and urine testing every four weeks starting at Week 4 as well as urine testing at follow-up visit and early withdrawal-visit. Pregnancy test results will be listed only.

Physical examination will be performed at screening, baseline, follow-up visit, early withdrawal-visit and several visits in between. Findings will be assigned by investigator to medical history, adverse event or serious adverse events.
Subjects with findings or subjects who missed examinations will be shown in a listing.

The following summaries will be provided:

- A summary of each vital sign parameter by randomised treatment group and time point
- A summary of the change from Baseline in each vital sign parameter by randomised treatment group and time point.
- Boxplots of the change from Baseline in each vital sign parameter by randomised treatment group and time point.
- A summary of the number and percentage for history of tobacco use and family history of cardiovascular risk factors by randomised treatment group.

Triplicate 12-lead ECGs will be obtained at screening, Week 12, 24, 52 and potential early withdrawal-visit. All ECG parameters will be calculated by taking the mean of the non-missing values obtained in the up to three 12-lead ECG evaluations at each visit.

The following summaries will be provided:

- A summary of each ECG parameter (i.e. heart rate, PR, QRS, QT, QTc) by randomised treatment group and time point
- A summary of the change from baseline in each ECG parameter by randomised treatment group and time point.

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- A summary of the number and percentage of subjects with abnormal findings for each ECG parameter by randomised treatment group and time point.
- A summary of the number and percentage of subjects with QTc interval exceeding >450ms/ >480ms/ >500ms by randomised treatment group and time point.
- A summary of the number and percentage of subjects with change from baseline in QTcF interval exceeding >30ms/ >60ms by randomised treatment group and time point.
- Boxplots of the change from baseline for each ECG parameter by randomised treatment group and time point.

By-subject listings of vital sign parameters, and ECG results (individual and average) and any other observations related to safety will be provided.

4.10.11 Safety Monitoring

4.10.11.1   Data Review Committee

A DRC (consisting of external rheumatology, infectious disease and respiratory experts, and GSK study team members that have no involvement in the acquisition of the data or direct contact with sites) will review ongoing unblinded safety data from the study and unblinded efficacy data at the interim analyses.

The first DRC review of safety data will be conducted after approximately 10 subjects per arm have completed 5 weeks of treatment, and subsequent reviews will take place approximately every 12 weeks thereafter until the end of the study.

Output shells for DRC outputs are provided in a separate document and the following outputs will be produced for each DRC review:

- Summary of Withdrawals by Reason for Withdrawal
- Summary of Demography Characteristics – Age, Gender and Weight
- Concomitant Medication
- Concomitant Medication of subjects with serious infections
- Concomitant Medication of subjects with D_{LCO} Hemoglobin-corrected Percent of Predicted decrease >15% change from baseline
- Summary of Treatment Emergent AEs - Overview
- Summary of Treatment Emergent AEs by SOC and PT
- Summary of AEs Leading to Withdrawal
- Plot of Most Common Adverse Events and Relative Risk
- Summary of SAEs
- Summary of AESIs of Serious Infections, Opportunistic Infections, Neutropenia, and PAP
- Summary of Hypersensitivity and Injection Site Reactions
- Summary of persistent cough, dyspnea or D_{LCO} decrease
- Summary of Change from Baseline in D_{LCO} Hemoglobin-corrected Percent of Predicted
- Summary of Proportion of Subjects with a >15% Decrease from Baseline in D_{LCO} Hemoglobin-corrected Percent of Predicted

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- Summary Statistics of Haematology and Clinical Chemistry Values at Each Visit
- Distribution of Haemoglobin, Total WBCs, Neutrophil Counts, Platelet Counts, ALT, AST and Total Bilirubin by Visit and Treatment with Maximum over Time

For the interim efficacy analyses (when 90 subjects have completed 4 and 12 weeks of treatment) the time interval between subsequent reviews may deviate from the 12 weeks to combine these interim analyses with a safety review.

The decision to stop the study or randomisation to specific arms will be made by the DRC. Further details are given in the earlier sections of this RAP and will be included in the DRC Statistical Guidance document.

Unblinded efficacy data will also be reviewed if needed outside of the planned interim analyses to assess benefit/risk based on the safety findings. When possible, these reviews will be scheduled to align with planned safety reviews.

A vote of the DRC committee will be taken at the conclusion of each meeting of the DRC. Each meeting of the committee will be associated with an active recommendation of proceeding unchanged, modifying or terminating the study. Further details will be outlined in the DRC Charter.

4.10.11.2   Medical Monitoring

Medical monitoring will happen in form of monthly blinded data review meetings. Further details and the list of generated output can be found in the MDRP and the MMP.

4.10.12 Immunogenicity

Immunogenicity samples for determination of anti-drug-antibody (ADA) will be collected. Samples taken after dosing with GSK3196165 that have a value at or above the cut-point will be considered potentially treatment-emergent ADA-positive. Shift table from baseline to every assessment will be produced for the Immunogenicity population to assess the number of subjects going from:

1) negative → negative,
2) negative → positive,
3) positive → negative, and
4) positive → positive.

Serum analysis will be performed under the management of Immunogenicity and Clinical Immunology (ICI), GlaxoSmithKline. Serum will be tested for the presence of anti-GSK3196165 antibodies using the currently approved analytical methodology incorporating screening, confirmation and titration steps.
Anti-GSK3196165 Binding AB Detection (positive/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 AB Detection.

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A Listing of DAS28 values will be produced for all subjects who developed ADA in the study, including rheumatoid factor and ADA status by visit.

4.11 Patient Reported Outcome (PRO) Measures

Change over time and change from baseline in RA Symptom and Impact Diary measures will be summarised for subjects that are in the ITT population but separately for subjects that are in the Actigraphy Population and subjects that are not in the Actigraphy Population. Responses for each of the 16 questions from the RA Symptom and Impact Diary will be summarised by visit. A repeated measures analysis of change from baseline in RA Symptom and Impact Diary measures will be done as done for DAS28(CRP) and other continuous efficacy parameters.

4.11.1 Actigraphy Substudy

During enrolment, subjects have the option to consent to participate in a substudy that collects data using an accelerometer in addition to the RA Symptom and Impact diary. The objective of the actigraphy substudy is to explore how actigraphy measurements of physical activity correlate to disease activity. Table 9 lists the measures used to meet the protocol objectives.

Table 9 Actigraphy Measures

Characteristic	Measures
Physical activity:	• Percent time sedentary based on activity count cut-off* • Percent time walking* • Activity counts (i.e., total activity score) • Average walking speed for durations of walking >1 min (m/s) • Number of continuous walking periods from 2-10 min (w/ 1-30 second pause), 10-30 min (w/1-1 min pause), >30 min (w/1-1 min pause)
Morning stiffness:	• Average sit-to-stand time during 1st 30 min after waking* • Average lie-to-stand time during 1st 30 min after waking* • Average activity counts for 2 hours after waking • Average activity counts for 4 hours after waking
Sleep quality:	• Percent time lying down during night-time • Average number of nighttime movement episodes (per hour) • Night-time rest efficiency defined as time NOT moving relative to time lying at night* • Fragmentation indices (movement time (%) divided by the number of movement episodes during night-time rest, and average duration of movement episodes)*
RA Symptom and Impact Diary	• 13 Symptom questions and 3 Impact questions
* Measure is a change to or clarification of protocol wording.	

4.11.1.1 Accelerometer data collection

The accelerometer will be placed on the subject and returned to the site according to the Time and Events table in Table 1. Results will be assigned to a visit as shown in Table 10.

Table 10 Accelerometer Placement and Removal

Day of Placement*	Day of Removal*	Visit

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Day -7	Day 7	Baseline = Day -7 to Day -1 Week 1 = Day 1 to Day 7
Day 71	Day 85	Week 12
Day 155	Day 169	Week 24
Day 239	Day 253	Week 36
Day 351	Day 365	Week 52
* Day of placement and removal are approximations.		

The raw accelerometer data will be analysed using an RA-specific algorithm developed by GSK and Imperial College London. At present, the algorithms are exploratory and not validated. A simple measure of overall activity level, "counts", will be used as previously reported in the literature. Counts are a result of summing post-filtered accelerometer values into 1 minute epoch "chunks", and represent a mapping from the raw acceleration for this specific fixed time period. Hence the value of the counts will vary based on the frequency and intensity of the raw acceleration. Measures determined in one minute epochs are collapsed into hourly and daily or 24-hour periods. The processed data will be reported according to whether the measure is collected during the daytime or night time hours, or over a 24-hour period:

- 24-hour period: The following measures will be reported within 24-hour periods starting at midnight and ending at 11:59:59 pm: average walking speed for walking bouts >1 minute, average activity counts per minute, number of continuous walking periods with duration 2-10 minutes, 10-30 minutes and >30 minutes, average sit-to-stand time and lie-to-stand time during 1st 30 minutes of getting up in the morning, average activity counts for the 2 hours and 4 hours after getting up.
- Night time: The following measures will be reported from the time of going to bed for the night until arising from bed in the morning: number of night time movement episodes per hour, night time rest efficiency, and fragmentation indices.
- Day time: The following measures will be reported from the time of getting out of bed in the morning until going to bed for the night: percent time sedentary, percent time walking, percent time lying down.

Each measure will be reported once per 24-hour period or day/night time unit of time to obtain up to approximately 7 days of data for baseline and Week 1, and up to approximately 14 days of data for Weeks 12, 24, 36, and 52.

4.11.1.2 Endpoint derivation and summaries

The median of the distribution of the daily values for each measure will be calculated for each subject and visit. Similarly, the median of the distribution of the daily responses for each of the questions in the RA Symptom and Impact diary will be calculated for each subject and visit. The endpoint for each measure (except for continuous walking periods) will be defined as the change from baseline for the median values, calculated as post-baseline median minus baseline median, where baseline is defined in Table 10.

The median value and change from baseline in the median value for each actigraphy measure (excluding the number of continuous walking periods) and visit will be summarised with univariate statistics by actual treatment group, where visit data for subjects rescuing to the

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highest dose will be grouped separately from the subjects randomised to that dose. Boxplots of the change from baseline in the median value will be plotted by actual treatment group. If less than 30 subjects participate in the Actigraphy substudy, then individual subject line plots will be produced for percent time sedentary, percent time walking, night-time rest efficiency and average counts/minute instead, using symbols to identify responses obtained at the rescue dose. Additional plots may be generated post hoc for other endpoints.

The number and percentage of continuous walking periods from 2-10 minutes, 10-30 minutes and >30 minutes will be summarised with categories 1, 2, 3, and ≥4 at each visit. The median response and change from baseline for the median response for each question from the RA Symptom and Impact diary questions will be summarised in a table. These data will not be graphed.

To assess the relationship between physical activity and DAS28(CRP), a scatter plot of activity counts versus DAS28(CRP) score over time will be provided using symbols to differentiate actual treatment group at each visit and a vertical bar where DAS28(CRP)=2.6 to identify responders from nonresponders. If there is sufficient data, a plot of change from baseline in activity counts versus change from baseline in DAS28(CRP) score over time and by DAS28(CRP) remission status will be provided instead of plots of the observed data using symbols to differentiate dose at each visit. Similarly, average walking speed versus DAS28(CRP) and night time rest efficiency versus DAS28(CRP) will be provided. The relationship between physical activity measures and ACR or biomarkers will not be investigated as stated in the protocol.

Plots will also be provided for the following efficacy endpoints versus questions from the RA Symptom and Impact diary by visit and by DAS28(CRP) remission status for all actigraphy subjects combined, using symbols to identify responses obtained at the rescue dose:
- Median percent time sedentary vs median Symptom Question 4 (worst pain while walking)
- Median activity counts vs median Symptom Question 8 (amount of energy)
- Median average sit-to-stand time vs median Symptom Question 1 (worst pain when sitting)
- Median average lie-to-stand time vs median Symptom Question 11 (early morning stiffness severity)
- Median night time rest efficiency vs median Symptom Question 2 (worst pain lying down)
- Median night time rest efficiency vs median Impact Question 2 (quality of sleep)
- Median functional index 1 (movement % / movement episodes) vs median Impact Question 3 (sleep affected by joint pain)
- Median functional index 2 (average duration of movement episodes) vs median Impact Question 3 (sleep affected by joint pain)

The results from these analyses will be reported after the Final analysis in a separate deliverable.

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4.12 Other Analyses

4.12.1 Pharmacokinetic Analysis

A population PK model of GSK3196165 will be developed based on PK data from the current study as well as the 5 studies in healthy, RA and MS adult subjects (MSC1000, MOR103C104, MSC1001 and MOR103C103)
The main objectives of this analysis are as follows:
- To develop a population pharmacokinetic model that describes the single- and repeat-dose pharmacokinetics of GSK3196165 following intravenous (IV) and SC administration in healthy subjects and subjects with rheumatoid arthritis and multiple sclerosis;
- To identify covariates that may influence pharmacokinetics of GSK3196165;
- To derive post-hoc estimates of individual pharmacokinetic parameters characterising the PK time profile of GSK3196165 for any given dose

Further details on the population PK analysis are provided in a separate technical Analysis Plan (Population Pharmacokinetic Analysis of GSK3196165 Following Intravenous and Subcutaneous Administration to Healthy Volunteers, Subjects with Rheumatoid Arthritis and Multiple Sclerosis (Date: 08-Jan-2016)).

4.12.2 Pharmacokinetic / Pharmacodynamic (PK/PD) Exploratory Analysis

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 post-hoc estimates from the PK model, and the response is characterised by the individual values of the pharmacodynamic markers or efficacy (e.g. DAS28(CRP)) or safety endpoints (e.g. AE of special interest, lung damage biomarkers).

Example of PK/PD graphs:
- Linear scatterplot of change from baseline in CRP levels at week 12 versus steady-state average concentration values (C_{ave}) estimated from the PK model
- Linear scatterplot of change from baseline in CRP levels at each visit versus pre-dose concentration values (C_{trough}) at corresponding visit estimated from the PK model
- Linear scatterplot of change from baseline in DAS28(CRP) measures at week 12 versus C_{ave} estimated from the PK model
- Linear scatterplot of change from baseline in DAS28(CRP) measures at each visit versus C_{trough} at corresponding visit estimated from the PK model
- Boxplot of C_{ave} stratified by ACR20 at Week 12
- Boxplot of C_{ave} stratified by ACR50 at Week 12
- Boxplot of C_{ave} stratified by ACR70 at Week 12
- Boxplot of C_{ave} stratified by AE status

A separate PK/PD RAP will be created to define further detail of the PK/PD analysis.

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4.12.3 Biomarkers

Analyses of biomarkers will be defined in a separate analysis plan.

4.12.4 Genetic Research

Analyses of genetics will be defined in a separate analysis plan, if deemed necessary.

4.13 Determination of Sample Size

The sample size assumptions outlined below for the primary objective assume that all doses are carried through to the end of the study, although there is the option to stop randomisation to doses following the interim analyses if clinical response criteria are not met, therefore the sample size gives the minimum number of subjects per arm.
The following sample size assumptions have been applied for the primary analysis and the dose response analysis:

4.13.1 Primary Analysis

The sample size for the primary analysis and hence the overall sample size for the study is based on detecting a 30% difference from placebo in the proportion of subjects in remission (DAS28 score <2.6) at Week 24 of the 52 week double-blind treatment period for each GSK3196165 dose.

Using a Fisher's exact test, a sample size of 35 subjects per arm will provide approximately 90% power to detect a difference of 30% in the proportion of subjects in remission between each GSK3196165 dose (33%) and placebo (3%) at the two-sided $\alpha=0.05$ level at 24 weeks. The placebo rate of 3% is based on a literature review of current therapies presenting DAS28(CRP) remission results. No adjustments will be made to the sample size to account for the multiple doses in this Phase 2 study.

The least significant difference this sample size will detect is an approximate 17% difference from placebo.

The sample size will not be increased to account for dropouts and all dropouts within the treatment period will be classed as non-remitters for the primary analysis.

4.13.2 Dose Response Analysis

It is estimated the dose response analysis can be conducted once a minimum of 15 subjects in each of the six treatment groups complete 12 weeks of treatment. Other analyses at earlier time points may also be conducted. The sample size has been estimated using simulation.

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The anticipated dose response curve assuming the numbers summarised below, and the precision around it was obtained through 100000 simulations where the following changes from baseline in DAS28(CRP) have been assumed at each dose level, with a between subject standard deviation of 1 (based on Phase 2 data in a DMARD-IR population):

Table 9 Assumed Change from Baseline in DAS28(CRP) Responses at 12 Weeks

Treatment	Placebo	22.5 mg	45 mg	90 mg	135 mg	180 mg
DAS28(CRP) change from baseline	-1.0	-1.54	-1.83	-2.1	-2.24	-2.32
N	N=15	N=15	N=15	N=15	N=15	N=15

The assumed change from baseline in DAS28(CRP) of 1.0 points on the placebo arm is based on a review of studies in a DMARD-IR population.

It is expected that the shape of the dose response curve will be sigmoidal and the data for the DAS28(CRP) change from baseline was simulated assuming the following three parameter Emax model:

$$Y = E_0 + E_{max} * [Di /\{ ED_{50} + Di \}]$$

Where E_0 is the minimum dose effect, E_{max} is the maximum achievable effect above E_0, ED_{50} is the dose at half E_{max} and Di are the doses = 0, 22.5, 45, 90, 135 and 180 mg. Y is a measure of DAS28(CRP) change from baseline. In this case the E_0 is the assumed effect with Dose=0 (placebo) which is -1.0 and the E_{max} is taken as -1.65, the maximum achievable effect above placebo.

Figure 1 shows the first 100 prediction curves (from 100000 simulations) and the overall median curve with the assumptions outlined above, illustrating the anticipated dose response curve with 15 subjects per arm. The black vertical intervals around each dose represent the change from baseline in DAS28(CRP) that are the 2.5 and 97.5 percentile values from all simulations.

The following table displays the proportion of simulations that are within a precision of 0.45 units in the change from baseline in DAS28(CRP) at each dose, with 15 subjects per arm. For the 135mg dose this is 98.9%.

Table 10 Proportion of Simulations that are Within a Precision of 0.45 Units in the Change from Baseline in DAS28(CRP) at each Dose

22.5 mg	45 mg	90 mg	135 mg	180 mg
90.4%	97.9%	98.8%	98.9%	95%

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Figure 1 Plot of the First 100 Prediction Curves with the Overall Median Curve at the Dose Response Analysis

Plot of first 100 prediction curves with overall median curve.
With 15, 15, 15, 15, 15, 15 subjects at 0, 22, 45, 90, 135, 180 doses respectively. SD = 1
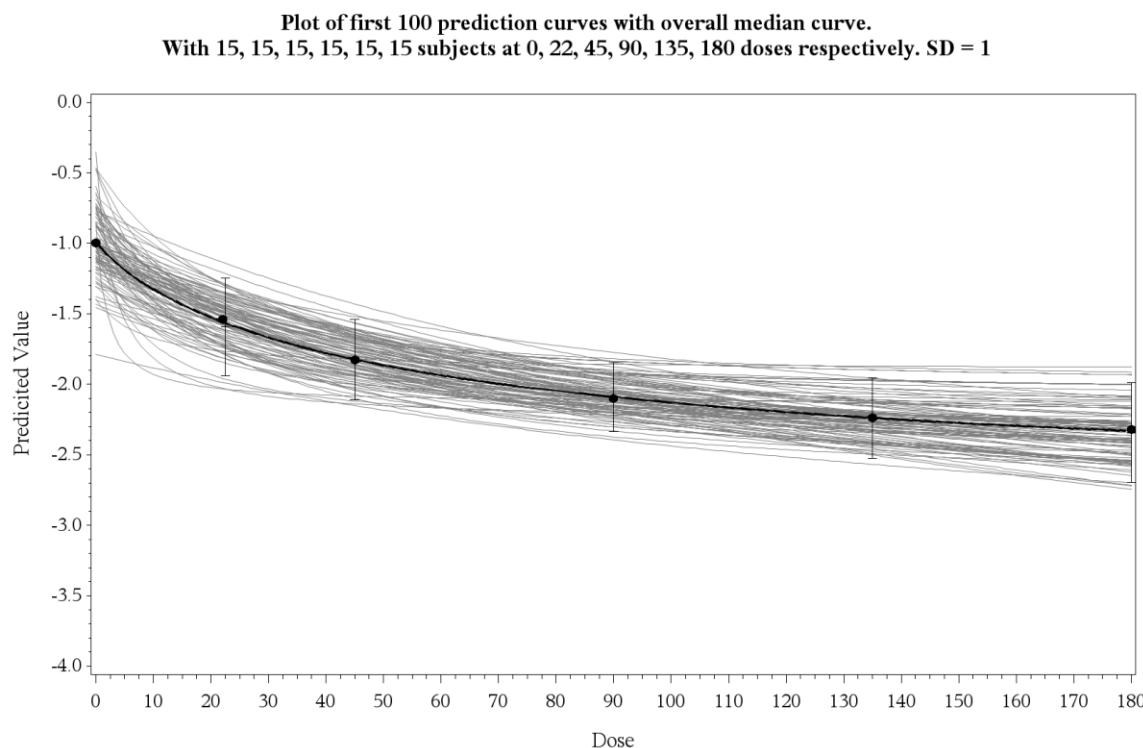
4.13.3 Sample Size Sensitivity for Primary Analysis

The power of the study will be affected by changes from the assumed remission rate and the table below shows the effect on power under varying remission rates on both MTX and GSK3196165 assuming a fixed sample size of 35 per arm.

Table 11 Power for Remission at 24 Weeks under Varying Remission Rates on MTX and GSK3196165:

MTX Remission Rate	GSK3196165 Remission Rate		
	25%	**33%**	**45%**
3%	69%	90%	99%
10%	27%	57%	89%
15%	12%	32%	73%

4.13.4 Sample Size Sensitivity for Dose Response Analysis

A key aspect of determining the sample size to assess dose response is the precision around the model estimates of the response (change from baseline on the DAS28(CRP)). The following Table outlines the proportion of simulations that are within a precision of 0.45 units in the change from baseline in DAS28(CRP) at the 22.5 mg and 135 mg dose groups for different estimates of the sample size and different values of the SD estimate, following 10000 simulations.

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Table 12 Proportion of Simulations that are Within a Precision of 0.45 Units in the Change from Baseline in DAS28(CRP) at the 22.5 and 135 mg Dose Groups Following 10000 Simulations

SD Estimate	N per Treatment group	Proportion 22.5 mg	Proportion 135 mg
0.7	10	98.4%	99.7%
	13	99.8%	99.9%
	15	99.9%	99.9%
1.0	10	61.5%	96.5%
	13	81.8%	98.2%
	15	**90.3%**	**98.9%**
1.3	15	52.2%	94.7%
	20	73.4%	97.5%
	25	89.5%	98.4%

Table 10 gives the 2.5 and 97.5 percentiles around the median estimates of response (Change from baseline in DAS28(CRP)) at each dose level assuming 20 subjects per treatment group for differing values of the SD estimates following 10000 simulations.

Table 13 2.5 and 97.5 Percentiles around the Median Estimates of Response at each Dose Level Following 10000 Simulations

SD Estimate	Placebo	22.5 mg	45 mg	90 mg	135 mg	180 mg
0.7	-1.33, -0.64	-1.83, -1.33	-2.03, -1.61	-2.27, -1.92	-2.44, -2.03	-2.59, -2.08
1.0	-1.44, -0.49	-1.93, -1.24	-2.11, -1.54	-2.33, -1.85	-2.52, -1.95	-2.69, -1.99
1.3	-1.54, -0.34	-2.02, -1.17	-2.18, -1.47	-2.41, 1.78	-2.60, -1.88	-2.80, -1.93

4.14 Changes in the Conduct of the Study or Planned Analysis

Continuous efficacy results for subjects who rescue to 180 mg dose or exceed the amount of allowed corticosteroid use will be set to missing as opposed to an observed cases analysis.

The exploratory endpoint 'time to first sustained ($\geq$24 continuous weeks) DAS28(CRP) remission' was modified to the proportion of subjects with sustained DAS28(CRP) remission including the Week 52 visit. Similarly, the definition of 'Major Clinical Response' was modified to achieving ACR70 for $\geq$24 continuous weeks including the Week 52 visit.

The exploratory endpoint 'Time to sustained ($\geq$24 weeks) discontinuation of all systemic corticosteroids administered for RA' will not be investigated. Instead a summary of corticosteroid concomitant medications will be converted to prednisone equivalent units, and the change from baseline in average daily prednisone dose will be summarised by visit. The number and percentage of subjects with $\geq$25% decrease from baseline to $\leq$7.5 mg/day will be summarised at Weeks 12, 24, 36, 48 and 52.

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6   Appendix

6.1   Appendix A: Opportunistic Infections: MedDRA Preferred Terms

Opportunistic Infections: MedDRA Preferred Terms	
AIDS retinopathy	Herpes pharyngitis
Acid fast bacilli infection	Herpes sepsis
Acinetobacter bacteraemia	Herpes simplex
Acinetobacter infection	Herpes simplex cervicitis
Acquired immunodeficiency syndrome	Herpes simplex hepatitis
Actinomycosis	Herpes simplex meningoencephalitis
Actinomycotic abdominal infection	Herpes simplex otitis externa
Actinomycotic pulmonary infection	Herpes simplex test positive
Acute HIV infection	Herpes simplex virus conjunctivitis neonatal
Acute hepatitis B	Herpes simplex visceral
Acute hepatitis C	Herpes virus infection
Adrenal gland tuberculosis	Herpes zoster
Arthritis fungal	Herpes zoster cutaneous disseminated
Arthritis salmonella	Herpes zoster disseminated
Aspergilloma	Herpes zoster infection neurological
Aspergillosis oral	Herpes zoster meningitis
Aspergillus infection	Herpes zoster meningoencephalitis
Asymptomatic HIV infection	Herpes zoster meningomyelitis
Asymptomatic viral hepatitis	Herpes zoster necrotising retinopathy
Atypical mycobacterial infection	Herpes zoster oticus
Atypical mycobacterial lower respiratory tract infection	Herpes zoster pharyngitis
Atypical mycobacterial lymphadenitis	Histoplasmosis
Atypical mycobacterial pneumonia	Histoplasmosis cutaneous
Atypical mycobacterium pericarditis	Histoplasmosis disseminated
Bacterial parotitis	Human T-cell lymphocytic virus type II infection
BK virus infection	Human T-cell lymphotropic virus infection
Biliary tract infection cryptosporidial	Human T-cell lymphotropic virus type I infection
Biliary tract infection fungal	Human polyomavirus infection
Blastomycosis	Immune reconstitution inflammatory syndrome associated tuberculosis
Bone tuberculosis	Intestinal tuberculosis
Brachyspira infection	JC virus granule cell neuronopathy
Brain empyema	JC virus infection

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Opportunistic Infections: MedDRA Preferred Terms	
Bronchitis fungal	Joint tuberculosis
Bronchopulmonary aspergillosis	Kaposi's sarcoma
Bronchopulmonary aspergillosis allergic	Kaposi's sarcoma AIDS related
Brucella sepsis	Kaposi's varicelliform eruption
Brucellosis	Leptotrichia infection
Candida endophthalmitis	Listeria encephalitis
Candida infection	Listeria sepsis
Candida osteomyelitis	Listeriosis
Candida pneumonia	Lower respiratory tract herpes infection
Candida retinitis	Lower respiratory tract infection fungal
Candida sepsis	Lymph node tuberculosis
Cerebral aspergillosis	Lymphadenitis fungal
Cerebral fungal infection	Lymphoma AIDS related
Cerebral toxoplasmosis	Male genital tract tuberculosis
Choroid tubercles	Meningitis aspergillus
Chronic hepatitis	Meningitis candida
Chronic hepatitis C	Meningitis coccidioides
Coccidioides encephalitis	Meningitis cryptococcal
Coccidioidomycosis	Meningitis fungal
Colitis herpes	Meningitis herpes
Congenital HIV infection	Meningitis histoplasma
Congenital cytomegalovirus infection	Meningitis listeria
Congenital hepatitis B infection	Meningitis salmonella
Congenital herpes simplex infection	Meningitis toxoplasmal
Congenital toxoplasmosis	Meningitis tuberculous
Congenital tuberculosis	Meningoencephalitis herpes simplex neonatal
Congenital varicella infection	Meningoencephalitis herpetic
Conjunctivitis tuberculous	Minor cognitive motor disorder
Corynebacterium infection	Mucocutaneous candidiasis
Corynebacterium sepsis	Mycobacterial infection
Cryptococcal cutaneous infection	Mycobacterium abscessus infection
Cryptococcal fungaemia	Mycobacterium avium complex immune restoration disease
Cryptococcosis	Mycobacterium avium complex infection
Cryptosporidiosis infection	Mycobacterium chelonae infection
Cutaneous coccidioidomycosis	Mycobacterium fortuitum infection
Cutaneous tuberculosis	Mycobacterium kansasii infection
Cytomegalovirus chorioretinitis	Mycobacterium marinum infection
Cytomegalovirus colitis	Mycobacterium ulcerans infection
Cytomegalovirus duodenitis	Mycotic endophthalmitis

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Opportunistic Infections: MedDRA Preferred Terms	
Cytomegalovirus enteritis	Mycotoxicosis
Cytomegalovirus enterocolitis	Myocarditis mycotic
Cytomegalovirus gastritis	Myocarditis toxoplasmal
Cytomegalovirus gastroenteritis	Nasal herpes
Cytomegalovirus gastrointestinal infection	Necrotising fasciitis fungal
Cytomegalovirus gastrointestinal ulcer	Necrotising herpetic retinopathy
Cytomegalovirus infection	Neonatal candida infection
Cytomegalovirus mononucleosis	Neonatal mucocutaneous herpes simplex
Cytomegalovirus mucocutaneous ulcer	Neurocryptococcosis
Cytomegalovirus myelomeningoradiculitis	Neutropenic sepsis
Cytomegalovirus myocarditis	Nocardia sepsis
Cytomegalovirus oesophagitis	Nocardiosis
Cytomegalovirus pancreatitis	Oesophageal candidiasis
Cytomegalovirus pericarditis	Oesophageal tuberculosis
Cytomegalovirus syndrome	Ophthalmic herpes simplex
Cytomegalovirus urinary tract infection	Ophthalmic herpes zoster
Cytomegalovirus viraemia	Oro-pharyngeal aspergillosis
Disseminated cryptococcosis	Oropharyngeal candidiasis
Disseminated cytomegaloviral infection	Osteomyelitis blastomyces
Disseminated tuberculosis	Osteomyelitis fungal
Ear tuberculosis	Osteomyelitis salmonella
Eczema herpeticum	Overgrowth fungal
Encephalitis cytomegalovirus	Pancreatitis fungal
Encephalitis fungal	Paratyphoid fever
Encephalitis post immunisation	Pericarditis fungal
Encephalitis post varicella	Pericarditis histoplasma
End stage AIDS	Pericarditis tuberculous
Endocarditis candida	Perinatal HIV infection
Endocarditis histoplasma	Peritoneal candidiasis
Enterocolitis AIDS	Peritoneal tuberculosis
Enterocolitis fungal	Persistent generalised lymphadenopathy
Epididymitis blastomyces	Pneumocystis jirovecii infection
Epididymitis tuberculous	Pneumocystis jirovecii pneumonia
Epstein-Barr virus associated lymphoma	Pneumonia blastomyces
Erythema induratum	Pneumonia cytomegaloviral
Erythrasma	Pneumonia fungal
Exanthema subitum	Pneumonia herpes viral
Extrapulmonary tuberculosis	Pneumonia salmonella
Eye infection toxoplasmal	Pneumonia toxoplasmal
Female genital tract tuberculosis	Polyomavirus-associated nephropathy

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Opportunistic Infections: MedDRA Preferred Terms	
Fungaemia	Presumed ocular histoplasmosis syndrome
Fungal abscess central nervous system	Proctitis herpes
Fungal endocarditis	Proctitis monilial
Fungal infection	Progressive multifocal leukoencephalopathy
Fungal oesophagitis	Prostatitis tuberculous
Fungal peritonitis	Pulmonary mycosis
Fungal sepsis	Pulmonary trichosporonosis
Fungal tracheitis	Pulmonary tuberculoma
Funguria	Pulmonary tuberculosis
Gastritis fungal	Pyelonephritis fungal
Gastritis herpes	Renal tuberculosis
Gastroenteritis cryptococcal	Respiratory moniliasis
Gastroenteritis cryptosporidial	Respiratory tract infection fungal
Gastrointestinal candidiasis	Retinitis histoplasma
Gastrointestinal fungal infection	Retroviral infection
Genital blister	Retroviral rebound syndrome
Genital herpes	Salmonella bacteraemia
Genital herpes zoster	Salmonella sepsis
Haemorrhagic pneumonia	Salmonellosis
Hepatosplenic abscess	Salpingitis tuberculous
HIV associated nephropathy	Silicotuberculosis
HIV cardiomyopathy	Sinusitis aspergillus
HIV enteropathy	Skin candida
HIV infection	Spleen tuberculosis
HIV infection CDC Group I	Splenic candidiasis
HIV infection CDC Group II	Splenic infection fungal
HIV infection CDC Group III	Stoma site candida
HIV infection CDC Group IV subgroup A	Stoma site infection
HIV infection CDC Group IV subgroup B	Superinfection fungal
HIV infection CDC Group IV subgroup C1	Superinfection mycobacterial
HIV infection CDC Group IV subgroup C2	Systemic candida
HIV infection CDC Group IV subgroup D	Systemic mycosis
HIV infection CDC Group IV subgroup E	T-cell lymphoma
HIV infection CDC category A	T-cell type acute leukaemia
HIV infection CDC category B	Thyroid tuberculosis
HIV infection CDC category C	Tongue fungal infection
HIV infection CDC group IV	Toxoplasmosis
HIV infection WHO clinical stage I	Tropical spastic paresis
HIV infection WHO clinical stage II	Tuberculoma of central nervous system

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Opportunistic Infections: MedDRA Preferred Terms	
HIV infection WHO clinical stage III	Tuberculosis
HIV infection WHO clinical stage IV	Tuberculosis bladder
HIV peripheral neuropathy	Tuberculosis gastrointestinal
HIV wasting syndrome	Tuberculosis liver
Hepatic candidiasis	Tuberculosis of central nervous system
Hepatic infection fungal	Tuberculosis of eye
Hepatitis B	Tuberculosis of genitourinary system
Hepatitis C	Tuberculosis of intrathoracic lymph nodes
Hepatitis chronic persistent	Tuberculosis of peripheral lymph nodes
Hepatitis fulminant	Tuberculosis ureter
Hepatitis toxoplasmal	Tuberculous abscess central nervous system
Hepatitis viral	Tuberculous endometritis
Hepatitis virus-associated nephropathy	Tuberculous laryngitis
Hepatosplenic candidiasis	Tuberculous pleurisy
Herpes dermatitis	Tuberculous tenosynovitis
Herpes oesophagitis	Typhoid fever
Herpes ophthalmic	Varicella keratitis

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6.2   Appendix B: Laboratory Parameters of Interest

Lab parameters of interest	Grade			
	1	2	3	4
HEMOGLOBIN decrease	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
WHITE CELL COUNT decrease	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
TOTAL NEUTROPHILS ABSOLUTE COUNT	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
LYMPHOCYTES ABSOLUTE COUNT decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
LYMPHOCYTES ABSOLUTE increased		>4000/mm3 - 20,000/mm3 ; >4-2 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	
PLATELET COUNT	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
CREATININE	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN x ULN	>6.0 x ULN
SODIUM decrease	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L;
SODIUM increase	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
POTASSIUM decrease	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
POTASSIUM increase	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L

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CALCIUM increase	>ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L;	>13.5 mg/dL; >3.4 mmol/L
CALCIUM decrease	<LLN - 1.0 mmol/L	<1.0 - 0.9 mmol/L	<0.9 - 0.8 mmol/L	<0.8 mmol/L
PHOSPHORUS INORGANIC	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L
ASAT (SGOT)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALAT (SGPT)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
GGT	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALKALINE PHOSPHATASE	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
BILIRUBIN, TOTAL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
CPK, TOTAL	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
ALBUMIN	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
GLUCOSE	>ULN -160 mg/dL; >ULN - 8.9 mmol/L	>160 -250 mg/dL; >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8	>500 mg/dL; >27.8 mmol/L
EST.CREATININE CLEARANCE	<LLN - 60 ml/min/1.73 m2	59 - 30 ml/min/1.73 m2	29 - 15 ml/min/1.73 m2	<15 ml/min/1.73 m2

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