TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol Amendment

Title:	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.

Compound Number: GSK3196165

Development Phase: IIB

Effective Date: 11-MAR-2016

Subject: Rheumatoid Arthritis, GSK3196165, DMARD-IR.

Protocol Amendment Number: 07

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N210890_00	2014-DEC-12	Original
2014N210890_01	2015-FEB-27	Amendment 1
This amendment includes removal of the Medical Monitor Contact Information on the Sponsor Information page, missing assessments in Section 7.1, and removal of example PRO Questionnaires as Appendix 12.7.		
2014N210890_02	2015-MAR-13	Amendment 2
This amendment includes revision of the study title on the Title page, clarification that actigraphy will only be at participating sites in Section 3, Section 7.2, Section 7.3, Section 7.10.5, Section 7.10.6, Appendix 12.7, minor revisions to placebo and co-medications information in Section 6.1, changes to the guidance on dosing instructions in Section 6.1, and revisions of anchors for Global Assessment of Arthritis in Section 7.3.2.		
2014N210890_03	2015-MAY-01	Amendment 3
This amendment includes removal of flow cytometry assessments from Section 3, 7.1 and Section 7.7, clarification of biomarkers in Section 3, corrections to neutropenia levels in Section 4.7.1, clarification of TB testing in Section 5.1 and Section 7.2, changes to administration of MTX in Section 6.1 and Section 6.9.2, clarification of unblinded administrator in Section 6.5, compliance of MTX in Section 6.8, and corrected Routine Laboratory Assessments in Section 7.4.11 (Table 2).		
2014N210890_04	2015-MAY-01	Amendment 4
This amendment includes removal of blank line in Section 7.1.		
2014N210890_05	2015-OCT-20	Amendment 5
This amendment includes additional criteria for continuation or withdrawal in the study at Week 38 in Section 4.2 and Section 5.4, clarification that SoC is standard of care in Section 4.5, clarification of rescreening procedure in Section 5.3.1, Section 5.3.2.2, clarification of D_{LCO} retesting in Section 5.3.2, addition of lipid measurements in Section 7.1 and Section 7.4.11 (Table 2), clarification of header version numbers and footnotes in Section 7.1, clarification of eligibility in Section 7.3.5, clarification of pregnancy in Section 7.4.7, additions to Appendix 12.1, revisions of Appendix 12.2 and Appendix 12.5, and added Appendix 12.9 to track all protocol text changes.		
2014N210890_06	2015-NOV-25	Amendment 6
This amendment includes clarification that the D_{LCO} tests may be repeated twice within the screening period in Section 5.1, clarification that only Fridericia's formula (QTcF) will be used in Section 5.2 and Section 5.4.2, clarification that the screening ECG test may be repeated once in Section 5.3.2.3, clarification of footnotes in Section 7.1, removal of biomarker IL-22 measurement in Section 7.7, and reinsertion of contraception guidance inadvertently deleted in Appendix 12.2 of previous Amendment 5.		
2014N210890_07	2016-MAR-11	Amendment 7
This amendment includes correction of the example formula to calculate the EULAR good/moderate response at Week 12 and Week 36 in Section 4.2 and Section 6.4; confirmation of mandatory chest HRCT if D_{LCO} ≥60% to <70% predicted in Section 5.1, Section 5.3.2.2, Section 7.1 and Section 7.4.1; update to IB document number and added reference in Section 11.		

SPONSOR SIGNATORY:

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SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s):

EudraCT number – 2014-003453-34

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201755

- I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201755

Rationale

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 rheumatoid arthritis (RA).

Objectives and Endpoints

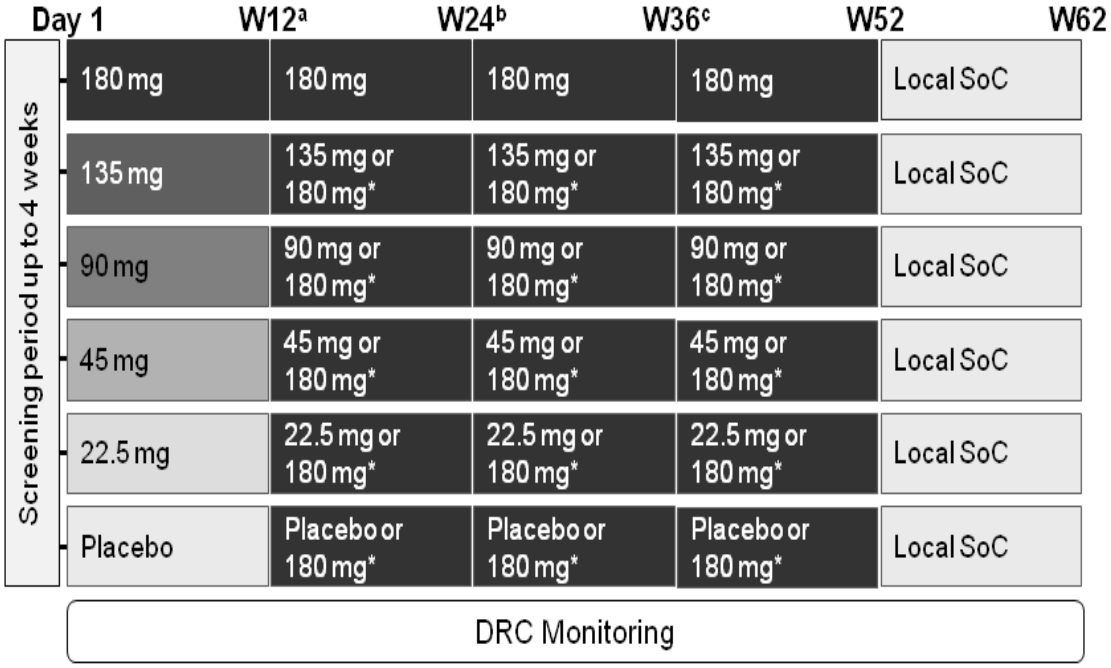
Objectives	Endpoints
Primary	
• To assess the efficacy of GSK3196165	• Proportion of subjects who achieve disease activity score for 28 different joints with CRP value (DAS28(CRP)) remission (DAS28 <2.6) at Week 24.
Secondary	
To assess • Dose-efficacy response of GSK3196165 • Safety • Population pharmacokinetics • Pharmacodynamics • Novel biomarkers ○ 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 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.

Objectives	Endpoints
	• 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.

Overall Design

This is a randomised, Phase IIb, dose-adaptive, multicentre, double-blind, parallel group, placebo-controlled study with the primary objective to assess the efficacy of GSK3196165, in combination with methotrexate (MTX), in subjects with active moderate-severe RA despite treatment with MTX.

Study design:



[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**

Treatment Arms and Duration

- Screening period up to four weeks, then 52 week combination dosing with rescue for subjects with insufficient response at Week 12 and Week 24, with a 12 week follow-up visit after the last dose.
- Five doses (22.5 mg, 45 mg, 90 mg, 135 mg and 180 mg) of GSK3196165 vs placebo given weekly for first five weeks, then every other week thereafter until Week 50.

Type and Number of Subjects

- Approximately 210 subjects with active moderate-severe rheumatoid arthritis despite treatment with methotrexate will be randomized.

Analysis

- The primary endpoint of the study is to evaluate the proportion of subjects that achieve DAS28(CRP) remission (DAS28 <2.6) following 24 weeks of treatment with GSK3196165 or matching placebo in adult subjects on concomitant MTX therapy.

- 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 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 DAS28(CRP) remission at Week 24.
- A key secondary objective is to evaluate the clinical dose response following 12 weeks of GSK3196165 treatment at 5 separate doses or placebo in adult subjects on concomitant MTX therapy.

2. INTRODUCTION

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).

2.1. Rationale

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 rheumatoid arthritis.

2.1.1. Rheumatoid Arthritis

RA is a chronic, systemic inflammatory autoimmune disease, characterised by a symmetrical polyarthritis that is associated with substantial disability and morbidity. RA affects approximately 0.5-1.0% of the worldwide population, primarily women, with a peak incidence of onset between 40 and 60 years of age.

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 (*e.g*. tumor necrosis factor α [TNFα], interleukin 6 [IL-6]), B-cells or T-cells. However, a substantial proportion of patients either fail to respond, or have inadequate response, to currently available RA therapies [Gaujoux-Viala, 2014; Nam, 2014]. 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.

2.1.2. GM-CSF and RA

GM-CSF, in combination with other inflammatory stimuli, can activate macrophages [Fleetwood, 2007; Mantovani, 2002], which produce a range of inflammatory cytokines, such as TNFα, IL-6, IL-1, IL-12p70 and IL-23 and various chemokines, and can also express class II MHC and present antigen to T cells, further contributing to the inflammatory process.

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 [Cornish, 2009]. GM-CSF induces the proliferation and activation of macrophage lineage cells leading to strongly increased production of key proinflammatory cytokines (including TNFα, IL-6, and IL-1), chemokines and matrix degrading proteases [Fleetwood, 2007; Gasson, 1991; Hamilton, 2004; Hamilton, 2013; Hart, 1991; Mantovani, 2007]. GM-CSF also serves as a differentiation factor for dendritic cells and induces upregulation of human lymphocyte antigen (HLA) class II on antigen presenting cells, which in turn will activate CD4+ T cells. In addition, GM-CSF is a strong chemo-attractant factor for neutrophils and induces the release of activated oxygen species from

neutrophils, which can directly damage cartilage structure [Dang, 1999; Gomez-Cambronero, 2003].

GM-CSF and its receptors are found abundantly in the synovial fluid, synovial tissue and plasma of patients with RA [Bell, 1995; Davis, 2010; Fiehn, 1992]. GM-CSF also contributes to osteoclastic bone resorption and subsequent joint damage [Nakano, 2007]. Synovial $CD68^{+}$ macrophages from RA patients correlate with disease activity scores and are potential biomarkers for treatment response [Bresnihan, 2009; Haringman, 2005]. The number of macrophages in synovial tissue is correlated with radiographic progression [Michelson, 1994; Mulherin, 1996]. In mouse models of collagen-induced arthritis (CIA), GM-CSF knockout or anti-GM-CSF treatment reduced disease activity and prevented progression of established arthritis and, furthermore administration of recombinant GM-CSF led to exacerbation of arthritis [Campbell, 1998; Cook, 2001; Plater-Zyberk, 2007; Yang, 2001].

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.

2.1.3. GSK3196165

GSK3196165 is a high-affinity recombinant human monoclonal antibody (mAb that binds specifically to human GM-CSF and neutralises its biological function by blocking the interaction of GM-CSF with its cell surface receptor [Steidl, 2008].

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 (IB) [GSK Document Number 2014N190256_01].

2.1.4. Clinical Data

GSK3196165 has been studied in 4 clinical trials to date as summarised in the IB GSK Document Number [2014N190256_01].

MSC-1001 was a Phase1b/2a multi-center, randomized, sequential group, double-blind, placebo-controlled study which evaluated the safety, preliminary efficacy, and PK of multiple doses of GSK3195165 in subjects (N=96) with active, mild-moderate RA [Behrens, 2014]. Previous treatment with biological/immunosuppressive therapies other than cell-depleting agents was allowed with an adequate washout period. Eligible patients had active moderate RA (1987 American College of Rheumatology [ACR] RA classification criteria, ≥3 swollen and ≥3 tender joints), an elevated CRP >5 mg/L (in sero-negative subjects) or CRP >2 mg/L (in RF and/or ACPA sero-positive subjects) and DAS28 score ≤5.1. Subjects received 4 IV weekly doses of GSK3195165 at 0.3 mg/kg, 1.0 mg/kg or 1.5 mg/kg or placebo in addition to stable concomitant treatment with DMARDs or low doses of oral corticosteroids. Rapid and significant reductions in disease activity (as measured by DAS28) were observed with the 1.0 mg/kg and 1.5 mg/kg doses. Greater reduction in disease activity to Week 4 was observed with 1.0 mg/kg than 1.5 mg/kg in this dose-escalation cohort study. A significant reduction in

mean DAS28 was not observed in the 0.3 mg/kg group. Other disease activity measures (*e.g.*, ACR response) and patient-reported outcomes were consistent with the results for DAS28. GSK3196165 was generally safe and well-tolerated in this study. Treatment emergent adverse events (AEs) in the GSK3195165 groups were mild or moderate in intensity and generally reported at frequencies similar to those in the placebo group. Infections were the most commonly reported AEs and occurred in 26.1% and 29.6% of GSK3196165 and placebo subjects, respectively. There was a numerical imbalance in cough (0/27 placebo, 3/69 active). There were no apparent trends in PFTs or D_{LCO} changes. In two cases, AEs were classified as serious because of hospitalization: paronychia in a placebo subject and pleurisy (which responded to antibiotics and therefore may have had an infectious etiology) in a GSK3195165 0.3 mg/kg subject. Both patients recovered.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To assess the efficacy of GSK3196165	• Proportion of subjects who achieve DAS28(CRP) remission (DAS28(CRP) <2.6) at Week 24.
Secondary	
To assess • Dose-efficacy response of GSK3196165 • Safety • Population pharmacokinetics • Pharmacodynamics • Novel biomarkers ○ 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 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

Objectives	Endpoints
	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
• Time to first sustained (≥24 continuous weeks) DAS28(CRP) remission. • Proportion of subjects achieving sustained (≥24 continuous weeks) DAS28(CRP) remission. • Proportion of subjects achieving Major Clinical Response (proportion of subjects achieving ACR70 for ≥24 continuous weeks). • Time to sustained (≥24 weeks) discontinuation of all systemic corticosteroids administered for RA. • 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.

4. STUDY DESIGN

4.1. Overall Design

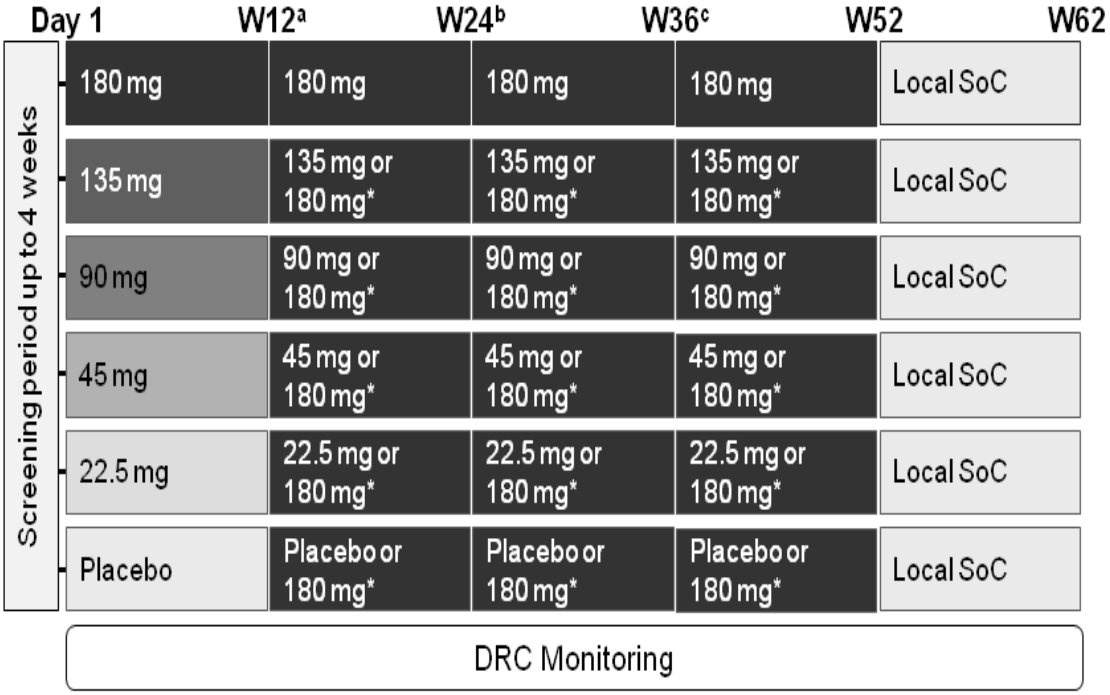
This is a randomised, Phase IIb, dose-adaptive, multicentre, double-blind, parallel group, placebo-controlled study with the primary objective to define the optimal therapeutic dose(s) of GSK3196165, in combination with MTX, in subjects with active moderate-severe RA despite treatment with MTX.

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 [Jones, 2010; Yazici, 2011]), 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.

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 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**

4.2. 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 EULAR good/moderate response* at Week 12.

***EULAR good or moderate response**

Week 12 DAS28(CRP)	DAS28(CRP) improvement from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good response	Moderate response	No response
>3.2 and ≤5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Source: [Fransen, 2005]

  - 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 [Smolen, 2014] and a review of response to MTX in randomised clinical studies [Boers, 2010].

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.

****EULAR good or moderate response**

Week 36 DAS28(CRP)	DAS28(CRP) improvement from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good response	Moderate response	No response
>3.2 and ≤5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Source: [Fransen, 2005]

4.3. 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. 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 decision to stop the study or randomisation to specific arms will be made by the DRC.

Interim analyses will be performed to assess futility and the dose-efficacy relationship once appropriate data are available. 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 are 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.

4.4. 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. Rescreening criteria are listed in the Study Reference Manual (SRM).

4.5. Design Justification

The overall study design is well established to assess the efficacy of a novel mAb, in combination with MTX, in subjects with active moderate-severe RA despite treatment with MTX. A key feature of the study is that interim analyses will be performed to assess futility and the dose-efficacy relationship once appropriate data are available. In addition, once the effective therapeutic dose(s) have been selected, treatment allocation may be adapted so that randomisation is stopped to the ineffective doses and future subjects are randomised to only the effective dose(s) and placebo.

Escape therapy is provided for subjects who have an inadequate response to treatment assessed at 12- and 24 weeks is aligned with routine standard of care. In addition, there is a mandatory withdrawal point at Week 38 to ensure that subjects do not experience prolonged exposure to an inadequate therapy.

The beneficial effect of sustained (*i.e.* ≥24 consecutive weeks) remission in comparison has been documented in numerous studies, in terms of reduction in radiographic progression as well as halting loss of physical function (Emery, 2014; Keystone, 2014; van Ingen, 2014), and EULAR/ACR have also recommended that sustained remission be reported in clinical trials (Aletaha, 2008). As such, the 52 week dosing period in this study provides an opportunity to assess the ability of GSK3196165 to induce sustained remission.

The proposed combination dosing duration of 52 weeks also facilitates a better assessment of tolerability and safety profile than a shorter duration.

4.6. Dose Rationale

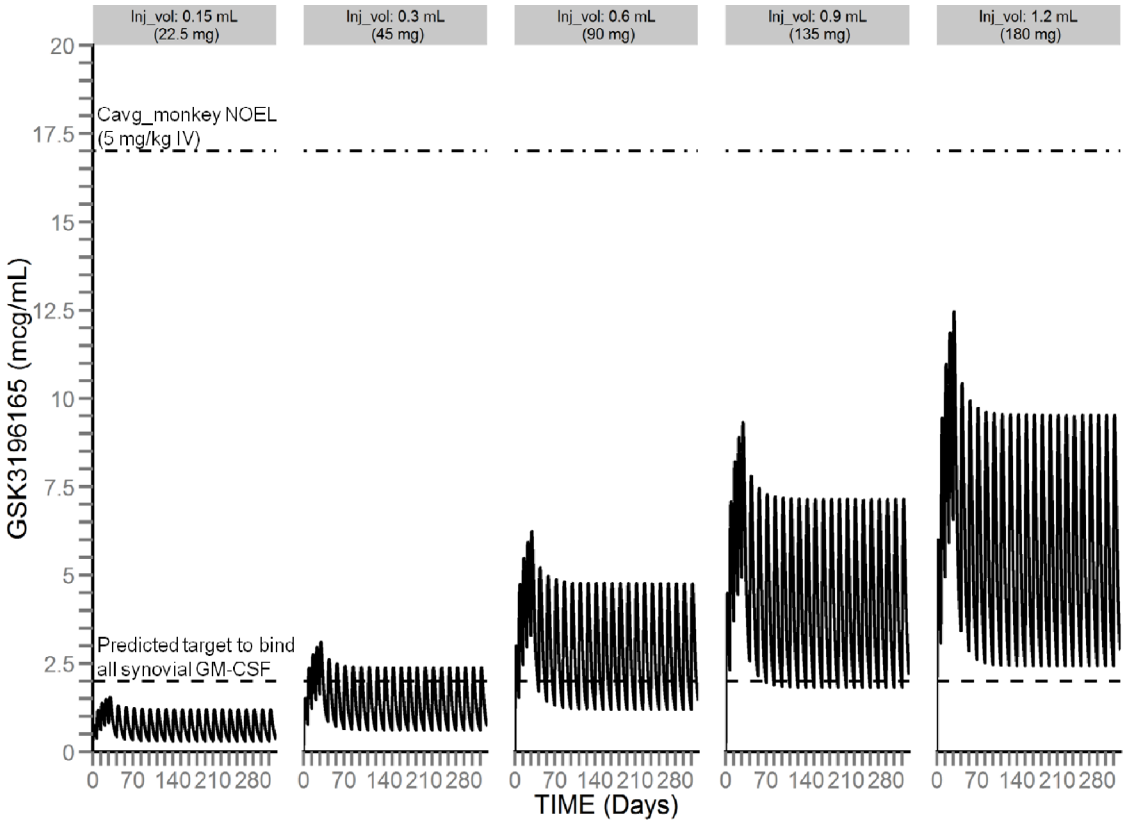
Complete inhibition of GM-CSF function by GSK3196165 has been observed in different assays in vitro at concentrations averaging 0.2 µg/mL. Although the level of penetration of GSK3196165 into the inflamed synovial tissues is not known, it is reasonable to assume that its penetration rate is in the range as seen with other mAbs. Concentration levels of mAbs in the synovium vary among patients and have been reported to be below 30% of the plasma values [Choy, 2000]. Based on a 30% penetration rate, the continuous GM-CSF production and considering patient heterogeneity, the minimal or sub-optimal clinical effect level is anticipated to be at approximately 10-fold higher (2 µg/mL) than the inhibitory concentration derived from in vitro studies.

4.6.1. Dose Recommendation

An eight-fold range of doses, that are expected to result in largely non-overlapping exposures, as well as placebo, are proposed for evaluation: placebo, 22.5 mg, 45 mg, 90 mg, 135 mg and 180 mg, with corresponding volumes of 0.15, 0.3, 0.6, 0.9, and 1.2 mL, respectively, which allow for ease of administration with standard syringes. Study agent will be administered SC weekly for 5 injections (Days 1, 8, 15, 22, 29), then EOW thereafter beginning at Day 43 (Week 6) and ending at Day 351 (Week 50). The doses of GSK3196165 have been selected based upon the results from previously conducted studies of the molecule.

A wide range of doses is being studied in order to fully characterise the dose response (Figure 1). The dose range includes doses that are anticipated to be effective or minimally effective based on the Phase 1b/2a RA study where IV doses of 1.0 mg/kg and 1.5 mg/kg showed activity and 0.3 mg/kg showed little to no activity after 4 weeks of treatment (see IB GSK Document Number [2014N190256_01]). Furthermore, doses of 90, 135, and 180 mg SC given every other week (EOW) are anticipated to result in steady state C_{min} concentration levels of approximately 2 µg/mL or greater (a hypothetical target to bind synovial GM-CSF based on in vitro data, and early clinical data, see IB GSK Document Number [2014N190256_01]). The weekly loading dose regimen is intended to achieve rapid reduction in disease activity, as supported by the completed 4 week RA study (MSC1001) where doses of 1.0 and 1.5 mg/kg IV weekly were associated with reduction of DAS28 score after the first dose that continued to decrease through Week 3 and 6, respectively (see IB GSK Document Number [2014N190256_01]).

Figure 1 Simulated GSK3196165 serum concentration-time profiles with 5 weekly doses followed by EOW dosing



Finally, the maximum dose proposed, 180 mg SC is comparable to approximately 1.2 mg/kg IV for a 70 kg individual, when bioavailability is taken into account. The maximum dose proposed, 180 mg, has been selected to allow ample margin to the No Adverse Effect level (NOAEL), and also a margin to the No Effect Level (NOEL) (the dose at which foamy alveolar macrophages were *not* observed in the 26-week rhesus monkey study). A dose of 180 mg SC is predicted to result in steady-state exposures which will allow a 26-fold margin to the NOAEL (50 mg/kg), where reversible minimal to mild foamy alveolar macrophages (considered non-adverse) were seen in the 26-week monkey toxicity study, with a 3-fold margin to the NOEL (5 mg/kg) (Table 1). The weekly dosing period is also supported by the completed RA study (MSC1001) where 4 weekly IV doses were generally well tolerated up to 1.5 mg/kg (approximately 225 mg SC in 70 kg patient).

Table 1 Safety margins with 180 mg SC GSK3196165 relative to exposures in nonclinical toxicology studies

Study	Species	Assessment	Dose (mg/kg/wk)	$AUC_{(0-336)}$ µg.hr/mL[b]	Fold difference *vs.* QW (end of weekly dosing phase)	Fold difference *vs.* every other week dosing (steady state)
Repeat Dose Toxicology, 4 weeks IV	Rhesus Monkey	Week 4	5	8814	3.5	NA
			25	44500	18	
			100[c,d]	110201	44	
Repeat Dose Toxicology, 13 weeks SC	Cynomolgus Monkey	Week 13	10	7124	2.8	3.8
			30[d]	25870	**10**	**14**
			100[c]	75594	30	40
Repeat Dose Toxicology, 26 weeks IV	Rhesus Monkey	Week 26	5[d]	5704	**2.3**	**3.0**
			15	22528	9.0	12
			50[c]	48734	19	26
MSC-1000 and MOR103C104 single dose (IV & SC)[a]	Human	End of weekly dosing phase Days 28-42	180 mg weekly x5 SC	2515		
		Every other week at steady state Days 140-154	180 mg every other week SC	1873		

IV intravenous; SC subcutaneous

a Simulated mean AUC based on analysis of SC and IV data for doses ≥0.5 mg/kg from study MSC1000 (N=18) and study MOR103C104 (N=32) with a 2 compartment model and calculation of F by ratio of Cliv/CLSC with bioavailability of 44% (95% CI 37%-53%)

b As there were no significant differences on sampling occasions or gender differences within each primate study, the end of study mean AUC (0-168) values have been used and multiplied by 2 to obtain mean concentrations over a two week period

c No observed adverse effect dose level (NOAEL)

d No observed effect dose level (NOEL)

4.6.2. Placebo control

A placebo arm is included to measure the absolute effect of each dose tested thereby allowing a robust determination of DAS28(CRP) reduction and remission rates, and the dose-response. Inclusion of a placebo arm will also allow a more robust exploration of the safety profile and therapeutic index of GSK3196165 when given in combination with MTX.

4.6.3. Methotrexate background

All subjects will continue to receive MTX, and there are rescue options at specific timepoints built into the study design. In addition, the investigator can withdraw the subject from study at any time as clinically indicated, so subjects having insufficient benefit will not be inadequately treated.

4.7. Benefit:Risk Assessment

Since GSK3196165 is still in early development with limited efficacy and safety data available, an integrated Benefit/Risk evaluation has not been performed at this point in time. However, summaries of findings from both non-clinical and clinical studies conducted with GSK3196165 can be found in the IB GSK Document Number [2014N190256_01]. The following section outlines the potential risk assessment and mitigation strategy for this protocol:

4.7.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infections	Immune-modulating biologic drugs used in RA (such as anti-TNF agents) are associated with an increased risk of serious and opportunistic infections. Similarly, because of the role of GM-CSF in anti-infective immunity, GSK3196165 also has the potential to increase the risk of infection. **Non-clinical Data:** No changes in peripheral blood populations (lymphocytes, neutrophils, monocytes, eosinophils or basophils), phagocytic activity of peripheral blood polymorphonuclear cells (investigational endpoint in the 26 week study), T-cell dependent B-cell primary or secondary response, or circulating cytokine levels (26 week study) were observed. Studies in knock-out mice showed that GM-CSF deficiency (GM-CSF-/-) affects the ability of mice to control infection when infected with *M. tuberculosis* or pulmonary group B *streptococcus* [LeVine, 1999]. **Clinical Data:** One healthy volunteer in study MSC-1000 experienced septic shock secondary to pneumonia 29 days after receiving a single dose of IP at 1.5 mg/kg. Subject recovered after treatment with antibiotics, and the subject completed the study follow-up period as per protocol. One RA subject in study MSC-1001 experienced serious pleurisy which responded to antibiotics.	**Subject selection (see Section 5.1):** • Subjects with active infections, or a history of recent or recurrent infections are not permitted to enter the study. • Subjects with significant leukopenia are not permitted to enter the study. • Subjects will be screened for TB, HIV and Hepatitis B and C, and excluded from study participation if positive. • Investigators are expected to assess vaccination status, including against influenza and pneumococcus, according to local guidelines. **Subject monitoring:** • Serious infections and opportunistic infections are categorised as adverse events of special interest (AESIs). • Subjects will be monitored for infection similar to subjects receiving any immune-modulating biologic therapy for RA. Appropriate diagnostic tests will be considered during the study if clinically indicated to ensure appropriate safety monitoring. • Subjects will be instructed as to the signs and symptoms of infection, and to contact site personnel should they develop. This information will also be contained within the patient Informed Consent Form. **Withdrawal criteria:** • In the event of a serious or opportunistic infection, study medication should be discontinued and the subject withdrawn from the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		study.
Pulmonary alveolar proteinosis (PAP)	GM-CSF signalling is required to maintain the normal function of alveolar macrophages. Long-term absence of GM-CSF signalling (*e.g.*, via hereditary GM-CSF deficiency or development of anti-GM-CSF auto-antibodies) is known to cause the extremely rare condition of PAP, which is characterized by the accumulation of surfactant lipids and protein in the alveolar spaces, with resultant impairment in gas exchange. **Non-clinical Data:** Non-adverse minimal to mild foamy alveolar macrophage accumulation were noted in lungs of monkeys in the 13-week SC and 26-week IV toxicology studies, but reversible following off drug period. Dose levels at which foamy alveolar macrophages were not observed were identified in these studies. **Clinical Data:** No cases of PAP have been reported to date in the clinical development program. Furthermore evaluation of pulmonary function has not demonstrated any abnormalities in pulmonary functions.	**Subject selection (see Section 5.1):** • Subjects with history of clinically-significant respiratory diseases that required treatment and/or follow up, or chronic cough or dyspnea will not be permitted to enter the study. • Pulmonary function testing (spirometry, D_{LCO}) measurements) will be performed at baseline in order to exclude those subjects with moderate-severe impairment. **Dose Duration:** • The exposure duration to GSK3196165 in this study is 12 months. Although the time course of PAP development in humans is unknown, the published literature suggests that it requires full inhibition of GM-CSF for years before clinical manifestation of the disease can be detected (refer to IB GSK Document Number [2014N190256_01] for further details). Therefore, the risk of development of PAP in this study is anticipated to be low. **Subject Monitoring:** • Specific pulmonary assessments are a requirement of the study protocol: ○ Subjects will be assessed every visit for the development of cough and dyspnea, and will also have regular chest auscultation and pulse oximetry measurements. Persistent cough or dyspnea will be reported as an AESI. ○ Pulmonary function testing (spirometry and D_{LCO} measurements) will be performed at baseline, and then every 3 months during treatment and at the follow-up visit. Relative change in D_{LCO} >15% from baseline will be reported as an AESI if confirmed with three consecutive weekly tests. • In the event of clinically-significant pulmonary events, it is recommended

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		that the subject is referred to a pulmonologist for further assessment. The study drug should be suspended until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined and clinically significant events have been excluded by the pulmonologist. Suggested pulmonary assessment and management algorithms will be provided in a separate Pulmonary Safety Guidance Document in the SRM.
Hypersensitivity reactions, including anaphylaxis	There is a potential risk of hypersensitivity reactions, including anaphylaxis, during and following the administration of protein-based products, such as GSK3196165. **Clinical Data**: No allergic or acute systemic reactions have been observed to date in the clinical development program.	**Subject selection (see Section 5.1):** • Subjects with a history of sensitivity to any of the study treatments, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation, will not be permitted to enter the study. **Study treatment administration/Subject monitoring:** • All SC administrations will be performed at the clinical site. • Subjects will be required to remain monitored at the site for 1 hour after the injection for the first 3 injections, and then for 30 minutes for subsequent injections. • Subjects should be informed of the signs and symptoms of an acute hypersensitivity reaction, and be instructed to seek immediate medical care should they develop. This information will also be contained within the patient Informed Consent Form. • Should hypersensitivity or anaphylaxis occur, subjects should be managed appropriately per local guidelines/medical judgement. • Severe hypersensitivity or anaphylaxis are categorised as AESIs. **Withdrawal criteria:** • In the event of severe hypersensitivity

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		or anaphylaxis, study medication should be discontinued and the subject withdrawn from the study.
Injection site reactions	SC injections may be associated with local reactions (*e.g.*, swelling, induration, pain). **Non-clinical & Clinical Data:** No macroscopic or microscopic changes indicative of local injection site reactions were observed following IV or SC administration.	**Subject monitoring:** • Subjects should be monitored for injection site reactions throughout the study, and the information recorded in the eCRF. • Injection sites will be rotated. • Any clinically-significant event should be reported as an AE.
Neutropenia	Although there is a perceived theoretical risk that GM-CSF blockade may affect maturation of leukocytes and their precursors, mice lacking GM-CSF do not develop neutropenia or show any major perturbation of hematopoiesis [Stanley, 1994]. **Non-clinical & Clinical Data:** There have been no reports of neutropenia or decreases in leukocytes in the non-clinical and clinical GSK3196165 program.	**Subject selection (see Section 5.1):** • Subjects with significant leukopenia (≤3.0 x 10^9/L); thrombocytopenia (platelet count ≤100 x 10^9/L); neutropenia (absolute neutrophil count ≤1.5 x 10^9/L); lymphocytopenia (≤0.5 x 10^9/L) within 28 days prior to Day 1 are not permitted to enter the study. **Subject monitoring:** • A full blood count (with differential) will be performed at regular intervals throughout the study (ref. Time and Events Table, Section 7.1). • Neutropenia is categorised as an AESI.
Reproductive toxicity	Published studies performed with GM-CSF -/- mice have indicated that GM-CSF depletion potentially affects fertility, establishment of pregnancy and post partum development of offspring in the mouse. **Non-clinical data** No GSK3196165-related effects on female or male fertility were noted in the SC 13-week repeat dose monkey study at doses up to 100 mg/kg/week (highest dose tested). In addition no maternal, embryofoetal or effects on fertility were noted in the reproductive toxicology studies using the surrogate rat anti-mouse GM-CSF monoclonal antibody, 22E9. The effect on human pregnancy is unknown. **Clinical Data:** No HVs or RA subjects became pregnant during the studies, but one MS subject	**Subject selection (see Section 5.1):** • Male and female subjects will only be permitted to enter the study if they meet the contraception requirements detailed in inclusion criterion #10. • In addition, females of child bearing potential will undergo pregnancy testing at screening and at regular intervals during the study (ref. Time and Events Table, Section 7.1). **Withdrawal criteria:** • In the event of a pregnancy in a female subject in the study, study medication should be discontinued and the subject withdrawn from the study. **Other considerations** • Subject will be followed to determine the outcome of the pregnancy • Any pregnancy complication or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	was found to be pregnant during study MOR103C10301028 and received four 2.0 mg/kg doses, the pregnancy was terminated 2 weeks later by elective abortion.	elective termination of a pregnancy will be reported as an AE or SAE.
Malignancy	The risk of malignancy is increased in patients with RA. In addition, immunomodulatory therapies may increase the risk of malignancy. **Non-clinical & Clinical Data:** There have been no reports of malignancy in the non-clinical and clinical GSK3196165 program.	**Subject selection (see Section 5.1):** • Subjects with a history of malignant neoplasm within the last 10 years or breast cancer within the last 20 years, except for non-melanoma skin cancers that have been excised and cured or carcinoma *in situ* of the uterine cervix, will not be permitted to enter the study.

4.7.2. Benefit Assessment

GM-CSF plays a key role in initiation and progression of inflammation in RA and indirectly increases the destruction of the bone and cartilage. GSK3196165 binds human GM-CSF, inhibits GM-CSF mediated responses in vitro and reduces inflammatory responses in rat arthritis models. GSK3196165 has shown evidence of efficacy in a Phase 1b/2a trial in patients with active RA [Behrens, 2014]. In addition, mavrilimumab (an anti-GMCSF α-subunit receptor mAb), has also shown substantial activity in RA subjects who had an inadequate response to MTX in studies of up to 24 weeks of dosing [Burmester, 2013; Burmester, 2014]. These data support the clinical evaluation of GSK3196165 in subjects with RA.

4.7.3. Overall Benefit:Risk Conclusion

Current preclinical and clinical data with GSK3196165 indicates that it binds and inhibits the function of GM-CSF and that this inhibition may have clinical utility in the treatment of inflammatory and autoimmune diseases, such as RA. Data with mavrilimumab, an anti-GMCSF α-subunit receptor mAb, also supports this contention.

Key potential risks are those described above that may be associated with inhibition of GM-CSF (*e.g.*, pulmonary toxicity, infection) and those associated with administration of a therapeutic monoclonal antibody (*e.g.* allergic reactions). Robust and systematic safety monitoring will be undertaken in studies of GSK3196165 to proactively address and mitigate the potential risks. Recent data with mavrilimumab administered for 24 weeks in combination with MTX in subjects with active RA [Burmester, 2014] provides further support that targeting this pathway is associated with an acceptable benefit:risk profile.

Given the safety monitoring that has been put in place to minimize risk to subjects participating in clinical studies of GSK3196165, the potential risks identified are justified by the potential benefits that may be afforded to patients with RA.

In addition, in accordance with routine pharmacovigilance, the safety review team (SRT) will review blinded safety data, including clinical laboratory parameters and adverse events, approximately every 4 weeks during the period of study conduct and unblinded safety data will be reviewed by the DRC at scheduled intervals (see Section 10.8.1). Key safety data that meets predefined thresholds will be reviewed by the DRC and will be a trigger for further investigation into the data and an assessment of the overall benefit:risk. Full details of safety thresholds will be provided in the DRC charter.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB GSK Document Number [2014N190256_01].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential. In addition, investigators are expected to assess vaccination status, including against influenza and pneumococcus according to local guidelines.

The study aims to recruit up to approximately 40% of subjects with RA disease duration of <2 years.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

Subjects eligible for enrolment in the study must meet *all* of the following criteria:

[1] AGE
1. Age ≥18 years at the time of signing informed consent.

[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Meets ACR/EULAR 2010 RA Classification Criteria.
3. Functional class I, II or III defined by the 1992 ACR Classification of Functional Status in RA.
4. Disease duration of ≥12 weeks (time from onset of patient-reported symptoms of either pain or stiffness or swelling in hands, feet or wrists).
5. Swollen joint count of ≥4 (66-joint count) and tender joint count of ≥4 (68-joint count) at screening and at Day 1.
6. DAS28(CRP) ≥3.2 at screening and DAS28(ESR) ≥3.2 at Day 1.

7. C-Reactive Protein (CRP) ≥5.0 mg/L at screening.
8. Must have previously received MTX (15-25 mg weekly) for at least 12 weeks before screening, with no change in route of administration, with a stable and tolerated dose for ≥4 weeks prior to Day 1. A stable dose of MTX ≥7.5 mg/week is acceptable, if the MTX dose has been reduced for reasons of documented intolerance to MTX, e.g. hepatic or hematologic toxicity, or per local requirement.

[3] WEIGHT

9. Weight ≥45 kg.

[4] SEX

10. Male or female subjects are eligible to participate so long as they meet and agree to abide by the contraceptive criteria detailed in Appendix 12.2.

[5] INFORMED CONSENT

11. Written informed consent prior to any of the screening procedures including discontinuation of prohibited medications.

[6] OTHER SAFETY-RELATED

12. Willing to continue or initiate treatment with oral folic acid (at least 5 mg/week) or equivalent and be treated during the entire study (mandatory co-medication for MTX treatment).
13. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) ≥60%[a,b] predicted; forced expiratory volume in 1 second (FEV1) ≥70% predicted.
    [a.] Screening and Day 1 values within 10% of each other (the test may be repeated twice within the screening period, *i.e.* subjects may undergo a total of three D_{LCO} tests during the screening period).
    [b.] For subjects with D_{LCO} values ≥60% to <70%, a baseline chest HRCT must be performed during the screening period, and it is recommended that the subject be reviewed by a local pulmonologist to exclude significant pre-existing respiratory disease.
14. No evidence of active or latent infection with *Mycobacterium tuberculosis* (TB), as defined by all of the following:
    a. No history of active or latent TB infection irrespective of treatment status.
    b. A negative diagnostic TB test within 28 days of baseline (Day 1) defined as:
       i. A negative QuantiFERON Gold test or T-spot test (may be performed locally) (NB: 2 successive indeterminate QuantiFERON tests will be considered as a positive result).

    OR

ii. If QuantiFERON gold or T-spot test not approved or registered in country of participation, then a negative tuberculin skin test (TST) reaction as per local guidelines is required (it is strongly recommended that subjects with a history of BCG vaccination be tested with QuantiFERON gold test).

c. Chest X-ray within 12 weeks of Day 1, locally read by a radiologist, with no evidence of current or previous pulmonary tuberculosis.

NB: If there has been recent close contact with persons who have active TB prior to study enrolment the subject will be referred to a TB physician to undergo additional evaluation.

Refer to Section 6.11.1 for detailed information on permitted therapies.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Pregnant or lactating women.
2. History of other inflammatory rheumatological or autoimmune disorders, other than Sjögren's syndrome secondary to RA.
3. History of any respiratory disease which (in the opinion of the investigator) would compromise subject safety or the ability of the subject to complete the study (*e.g.* significant interstitial lung disease, such as pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), moderate-severe asthma, bronchiectasis, previous PAP).
4. Clinically-significant or unstable (in the opinion of the investigator) persistent cough or dyspnea that is unexplained.
5. QTc >450msec *or* QTc >480msec for subjects with bundle branch block. The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).
6. Liver function tests: alanine aminotransferase (ALT) >1.5x upper limit of normal (ULN); aspartate transaminase (AST) >1.5 upper limit of normal; alkaline phosphatase and bilirubin ≥1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
7. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).
8. Significant unstable or uncontrolled acute or chronic disease (*e.g.*, cardiovascular including uncompensated congestive cardiac failure NYHA III or IV, myocardial infarction within 12 months, unstable angina pectoris, uncontrolled hypertension, uncontrolled hypercholesterolemia) pulmonary, hematologic, gastrointestinal (including Crohn's Disease or ulcerative colitis), hepatic, renal, neurological, psychiatric, malignancy, endocrinological or infectious diseases, which, in the

opinion of the investigator, could confound the results of the study or put the subject at undue risk.

9. A history of malignant neoplasm within the last 10 years or breast cancer within the last 20 years, except for non-melanoma skin cancers that have been excised and cured or carcinoma *in situ* of the uterine cervix.
10. Kidney disease**:** Current or history of renal disease, or estimated creatinine clearance <60 mL/min/1.73m^2 or serum creatinine >1.5xULN within 28 days of Day 1.
11. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
12. History of infected joint prosthesis at any time, with the prosthesis still *in situ*. History of leg ulcers, catheters, chronic sinusitis or recurrent chest or urinary tract infections.
13. Active infections, or history of recurrent infections (excluding recurrent fungal infections of the nail bed), or have required management of acute or chronic infections, as follows:
    a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).

    OR

    b. Hospitalization for treatment of infection within 26 weeks of Day 1.

    OR

    c. Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 26 weeks of Day 1 or oral antimicrobials within 14 days of Day 1.
14. A vaccination (live or attenuated) within 30 days of Day 1 or BCG vaccination within 365 days of Day 1, or a live vaccination planned during the course of the study.
15. Any surgical procedure, including bone or joint surgery/synovectomy within 12 weeks prior to Day 1 or any planned surgery within the duration of the study or follow-up period.
16. For those subjects in the actigraphy substudy:
    - wheelchair, walking aids, artificial limbs
    - history of severe skin allergy
    - active implantable device
    - pacemaker.

[2] CONCOMITANT MEDICATIONS

17. Use of prohibited medications:

    Prior to AND throughout the study:

- Any conventional DMARDs other than MTX (including hydroxychloroquine,

sulphasalazine, minocycline, ciclosporin) should be withdrawn at least 2 weeks prior to Day 1.

- Subjects may require longer to discontinue azathioprine or leflunomide prior to randomization:
  - Azathioprine must be discontinued ≥28 days prior to randomization.
  - Leflunomide must be discontinued ≥12 weeks prior to randomization (or ≥14 days after 11 days of standard cholestyramine or activated charcoal washout).
- **For these subjects, written informed consent for the study (or sub-studies) must be obtained prior to beginning the screening period.** However, other screening assessments, other than consent, must occur within 28 days prior to randomization.

- Any biologic agents (such as TNF inhibitors such as adalimumab, etanercept, infliximab, certolizumab pegol, golimumab or non-TNF inhibitors (including abatacept, rituximab, tocilizumab, belimumab).
- Any anti-rheumatic investigational compounds.
- Any alkylating agents (such as cyclophosphamide or chlorambucil).
- Plasmapheresis or intravenous immunoglobulin (IVIG) within 26 weeks of Day 1.

18. Corticosteroids:

- Any IM, IV or IA corticosteroids within 8 weeks of Day 1.
- Oral corticosteroids:
  - Any treatment with >10 mg/day dose oral prednisolone (or equivalent) within 28 days of Day 1.
  - New oral corticosteroid or changes in corticosteroid dose within the 28 days prior to Day 1. (New topical steroids and immunosuppressive agents (*e.g.*, eye drops, creams) are permitted).

19. Non-steroidal anti-inflammatory drugs (NSAIDs):

- New or change in dose of NSAID within 14 days of Day 1.

20. Any non-anti-rheumatic investigational treatment must be discontinued for at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1.

[3] RELEVANT HABITS
21. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within a year prior to Day 1.

[4] CONTRAINDICATIONS
22. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical

Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
23. Abnormal chest X-ray within 12 weeks of Day 1 (locally read and reported by a radiologist) judged by the investigator as clinically-significant.
24. Any Grade 3 or 4 hematology or clinical chemistry laboratory abnormality [CTCAE, 2009 v4.0] within 28 days of Day 1.
25. Hemoglobin ≤9 g/dL; white blood cell count ≤3.0 x 10^9/L; platelet count ≤100 x 10^9/L; absolute neutrophil count ≤1.5 x 10^9/L; lymphocyte count ≤0.5 x 10^9/L within 28 days of Day 1.
26. Serologic evidence of current/previous Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg) and anti-Hepatitis B core (anti-HBc) antibody as follows within 28 days of Day 1: • Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
27. Hepatitis C: Positive test for Hepatitis C virus (HCV) antibody confirmed on a subsequent blood sample by RNA-PCR assay within 28 days of Day 1. • Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.
28. Positive serology for human immunodeficiency virus (HIV) 1 or 2 (within 28 days of Day 1).

5.3. Screening/Baseline Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

5.3.1. Re-Screening

If a subject has not met all of the Eligibility Criteria within the 28 day screening period, re-screening is required. Subjects are only allowed to be re-screened once; the entire screening process must be repeated (with the exception of chest X-ray if within 12 weeks of the first screening period or HRCT if this was already performed within the first screening period).

If a blood sample has to be withdrawn due to sample handling problems, breakage or sample integrity, this is not considered a re-screening.

Further details regarding the procedure for re-screening may be found in the SRM.

5.3.2. Re-Testing

5.3.2.1. Laboratory tests

If a subject fails any of the laboratory exclusion criteria, the test may be repeated twice within the screening period. If the subject fails the laboratory criteria for a third time they will be considered a screen failure; these subjects may be re-screened as described in Section 5.3.1.

If a blood sample has to be withdrawn due to sample handling problems, breakage or sample integrity, this is not considered a re-testing.

Further details regarding the procedure for laboratory re-testing may be found in the SRM.

5.3.2.2. D_{LCO} test

If the screening D_{LCO} value is ≥70% predicted, but the subsequent "Day 1" value is <70% but ≥60% predicted, the D_{LCO} test may 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.

5.3.2.3. ECG test

The ECG may be repeated once within the screening period if the recorded QTcF value was slightly out of range, and the Investigator does not consider that there are any other clinically-significant ECG abnormalities that would preclude the subject from participating in the study.

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Any subject that fails to achieve EULAR good/moderate response at Week 36 will not be dosed at Week 38, and will be withdrawn from the study; no further study treatment will be administered. A notification that the subject must be withdrawn will be sent to the investigator prior to the scheduled Week 38 visit.

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

In addition, study medications will be discontinued and the subject withdrawn from the study in the event of any of the following:

- All serious infections.
- Pregnancy.
- Confirmed PAP.
- Severe or serious hypersensitivity reactions, including anaphylaxis.
- If the liver chemistry stopping criteria (Section 5.4.1) or QTc stopping criteria (Section 5.4.2) are met.
- Persistent or recurrent hematological laboratory abnormalities (see Section 5.5.2).
- Other serious or severe adverse events, at the discretion of the investigator, after consultation with the Medical Monitor.

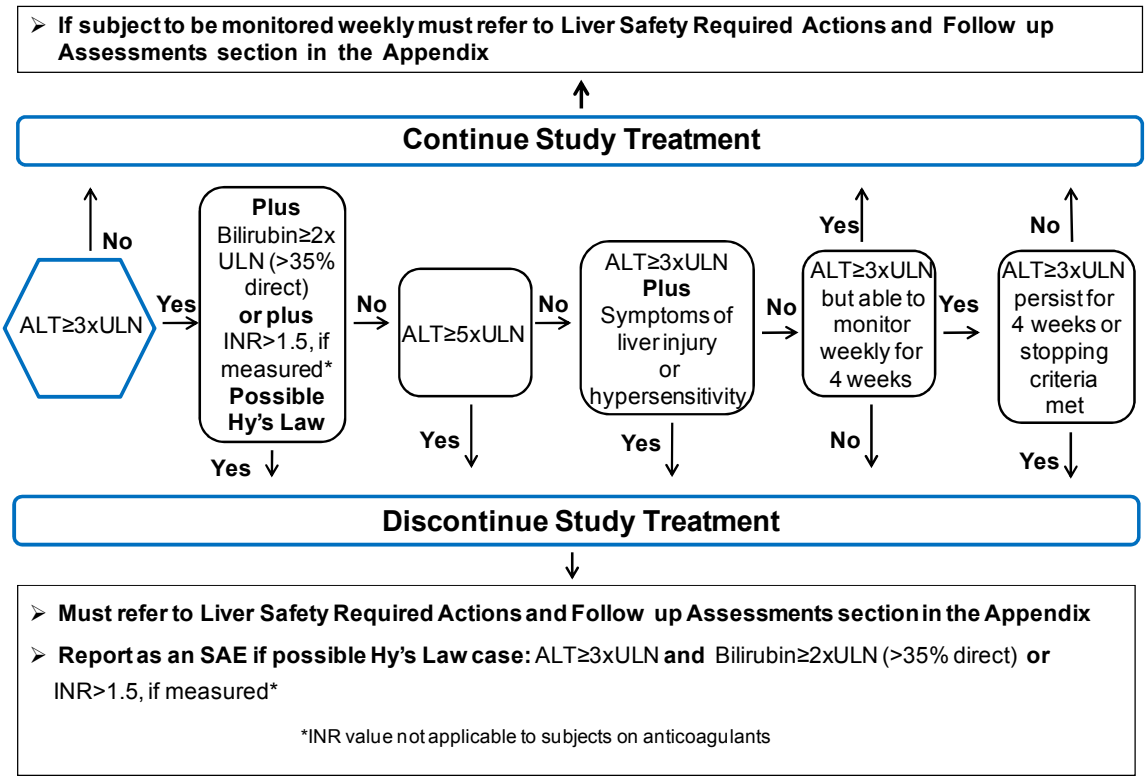
If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Any subject who withdraws must complete an early withdrawal visit and the 12 week follow-up visit.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) [FDA, 2009].

5.4.1.1. Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 12.3.

5.4.1.2. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

a. QTc >500 msec OR uncorrected QT >600 msec

b. Change from baseline of QTc >60 msec

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

For subjects with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with bundle branch block	**Discontinuation QTc with bundle branch block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

5.5. Treatment interruption

5.5.1. Respiratory Symptoms

Study medications will be temporarily suspended to allow investigation in the event of any of the following:

- Persistent reduction in D_{LCO} >15% relative decrease from baseline for three consecutive weeks.
- Persistent cough (CTC grade 2 or 3) or dyspnea (Borg scale grade 3 or above) for three consecutive weeks.

It is recommended that the subject be referred to a pulmonologist for further assessment. The study drug should be suspended until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined and clinically significant events have been excluded by the pulmonologist. As described in Section 5.4, a confirmed diagnosis of PAP necessitates permanent cessation of study medication and withdrawal of the subject from the study. Suggested pulmonary assessment and management algorithms are provided in a separate Pulmonary Safety Guidance Document in the SRM.

5.5.2. Hematologic abnormalities

The following haematological laboratory abnormalities require temporary suspension of study medications and prompt retesting, ideally within 3-5 days:

- White blood cell count <2.0 x 10^9/L
- Absolute neutrophil count <1.0 x 10^9/L
- Lymphocyte count <0.5 x 10^9/L

Study medication should not be restarted until the parameters are above these values, and subjects should be followed as appropriate until resolution of the event.

If these abnormalities are persistent (present on ≥2 sequential tests), or occur recurrently (on 2 separate occasions), study medications will be permanently discontinued and the subject withdrawn from the study.

5.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment		**Co-medication**
Product name:	GSK3196165	Placebo	Methotrexate and folic (or folinic) acid.
Function	Test (investigational product)	Control	Background treatment (started prior to and maintained during the study).
Formulation description:	See IB GSK Document Number [2014N190256_01] for details.	The placebo in this study will be sterile 0.9% (w/v) sodium chloride solution.	Variable. See labels for details.
Dosage form:	Liquid	Liquid	MTX: tablet or liquid Folic (or folinic) acid: capsule, tablet or liquid.
Dosage levels (volumes):	22.5 mg (0.15mL) 45 mg (0.3mL) 90 mg (0.6mL) 135 mg (0.9mL) 180 mg (1.2mL)	0.6 mL	MTX:7.5-25mg/week Folic (or folinic) acid: ≥5 mg/week. Note: Folic (or folinic) acid dose may be increased to counteract side-effects of MTX (including nausea, mucositis, and headache).
Route of Administration:	Investigational product should be administered SC into thigh or abdomen, sites should be rotated. Safety should be monitored for 1 hour after the injection, for the first 3 injections, then for 30 minutes thereafter. Such monitoring will include general safety monitoring including monitoring for systemic hypersensitivity infusion reactions and local injection site reactions. Trained rescue personnel and rescue medications/equipment must be available for use at all times.		MTX: oral or subcutaneous injection Folic (or folinic) acid: oral

	Study Treatment		**Co-medication**
Dosing instructions:	GSK3196165/placebo should be administered on the same day each week ± 1 day for the first 5 weekly doses (with a minimum of 5 days between doses, for no more than 2 consecutive doses). Following this GSK3196165/placebo should be administered on the same day EOW ± 3 days (with a minimum of 8 days between doses). GSK3196165/placebo will be discontinued or interrupted as described in Section 5.4 or Section 5.5. Subjects will be randomized as shown in Time and Events Table, Section 7.1, and the dosing schedule should be followed as closely as possible. The unblinded administrator (study co-ordinator or nurse) assigned to the study will be required to prepare and administer the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment randomly through an interactive response technology system (IRTS). Procedures must be in place to ensure the blind is maintained by any site staff involved in clinical care or assessment of the subject, and by the subject themselves. During the first 12 weeks of study every attempt should be made to ensure all doses are administered. After 12 weeks, up to 1 dose in an 8 week period may be missed, not to exceed 2 missed doses total over the 52 weeks of treatment. If at any time the subject misses 2 doses over 52 weeks, the Medical Monitor must be contacted for permission to continue study medication.		MTX: can be taken as a single weekly dose, or divided weekly dose, per investigator's discretion. Folic (or folinic) acid should be taken the day after and at least 12 hours following MTX administration.
Physical description:	Sterile, aqueous solution of purified monoclonal antibody 150 mg/mL	Sterile 0.9% (w/v) sodium chloride solution.	See label for details

	Study Treatment		**Co-medication**
Method for individualizing dosage:	22.5 and 45 mg doses - required volume will be drawn into a small, (*e.g.* 0.3 or 0.5 mL) syringe. 90 and 135 mg doses - required volume will be drawn into a small (*e.g.* 1 mL) syringe. 180 mg dose - required volume will be drawn into a small (*e.g.* 2 mL or 3 mL) syringe. The required volume should be dosed immediately.	A volume of 0.6 mL will be drawn into a small (*e.g.* 1 mL) syringe.	See label for details.

Investigators are responsible for ensuring that subjects continue to receive MTX and folic acid.

Timing of MTX is unrelated to food intake, and may be changed at the investigator's discretion in case of intolerability.

Subjects will receive ≥5 mg/week folic (or folinic) acid orally. The dosing regimen is at the discretion of the investigator. Folic (or folinic) acid should be taken the day after MTX administration and at least 12 hours following the MTX. Folic (or folinic) acid dose may be increased to counteract side-effects of MTX (including nausea, mucositis, and headache).

MTX dosing should be kept stable throughout the study as far as possible. Dose reduction is permitted to a minimum of 7.5 mg/week due to intolerance or toxicity, and dose increase, following reduction, is permitted back to the subject's dose prior to reduction (maximum dose 25 mg/week). Likewise, temporary interruption of MTX dosing for the management of intolerance will be permitted, and any reduction or interruption should be recorded, with the reason, in the eCRF.

All local standard-of-care practices for the administration of MTX, including laboratory testing, follow-up care, contraindications, and folic acid administration should be performed throughout the study.

6.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule.

The study will use central randomization and the randomization schedule will be generated by Clinical Statistics using validated randomization software. Once a randomization number has been assigned to a subject, it cannot be assigned to another subject in the study, even if the original subject withdraws before taking study medication.

Randomization numbers will be assigned to subjects using an Interactive Response Technology system (IRTS).

Subjects should be randomized and receive their first dose of study medications on the same day (Day 1).

6.3. Planned Dose Adjustments

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum dose will not exceed 180 mg.

6.4. Subject Specific Dose Adjustment Criteria

- "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 highest remaining) dose at Week 14 if they have failed to achieve EULAR good/moderate response* 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 highest remaining) dose of the study after the Interim Analysis) at Week 26 if their DAS28(CRP) score at this timepoint is >3.2.

***EULAR good or moderate response**

Week 12 DAS28(CRP)	DAS28(CRP) improvement from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good response	Moderate response	No response
>3.2 and ≤5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Source: [Fransen, 2005]

6.5. Blinding

The study will be double-blind, which means that the investigator and trial staff at site (apart from the unblinded administrator [study co-ordinator or nurse]), subject, and sponsor personnel who are not members of the DRC will be blinded to the trial treatment allocated to each individual subject.

There will be an unblinded administrator (study co-ordinator or nurse) that will prepare and administer the study treatment. A shield (*e.g.*, eye mask or blindfold) will be used during investigational product administration so that subjects are not able to see the

injection volume, syringe size, or any difference in color between GSK3196165 and placebo.

In this Phase 2b study, the DRC (see Section 10.8.1) will have access to unblinded data at a group level, but will not have individual subject level data.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the eCRF

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

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

6.6. Packaging and Labeling

The contents of the label for GSK3196165 will be in accordance with all applicable regulatory requirements for clinical supplies.

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only the unblinded administrator (study co-ordinator or nurse) may administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (*i.e.* receipt, reconciliation and final disposition records).

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.8. Compliance with Study Treatment Administration

GSK3196165 or placebo will be administered by subcutaneous injection to subjects at the site by the unblinded administrator (study co-ordinator or nurse). The date and time of each dose and volume administered in the clinic will be recorded in the eCRF.

Subjects will be given instructions on compliance and treatment with MTX. The date taken and total weekly dose will be recorded in the eCRF.

Folic (or folinic) acid must also be taken as instructed in Section 6.1.

6.9. Treatment of Study Treatment Overdose

6.9.1. Overdose of GSK3196165

There is very limited clinical safety data at this stage of development. However there have been no reports of overdose with GSK3196165 to date. The risk of overdose occurring is considered low because in GSK3196165 will be administered by an independent administrator, and the maximum volume that can be withdrawn from the vial is equivalent to the highest dose to be evaluated. No specific treatment is recommended for an overdose of GSK3196165, and the investigator should treat as clinically indicated. Details (amount of investigational product given and any resulting AEs/SAEs) should be recorded in the eCRF.

In the event of an overdose the investigator should:

- contact the Medical Monitor immediately
- closely monitor the subject for AEs/SAEs and laboratory abnormalities
- obtain a plasma sample for PK analysis at the time of the event, and three days after the event (unless otherwise requested by the Medical Monitor)
- consult with the Medical Monitor for any decisions regarding dose interruptions or modifications based on the clinical evaluation of the subject.

6.9.2. Overdose of Methotrexate

Refer to the local prescribing information for advice on treatment of MTX overdose. Some guidance is provided below.

Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral MTX have been reported. In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions. Folinic acid is a specific antidote for MTX and, following accidental overdosage, should be administered within one hour at a dosage equal to, or greater than, the MTX dose. It may be administered by IV bolus or infusion. Further doses may be required. The subject should be observed carefully and blood transfusions, renal dialysis and reverse barrier nursing may be necessary. In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of MTX and/or its metabolites in the renal tubules. Neither hemodialysis nor peritoneal dialysis has been shown to improve MTX elimination. Effective clearance of MTX has been reported with acute, intermittent hemodialysis using a high flux dialyser.

6.10. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.11. Concomitant Medications and Non-Drug Therapies

During the past decade, the ability of pro-inflammatory cytokines to alter the expression and activity of drug metabolising enzymes has become increasingly evident [Lee, 2010; Zhou, 2011; Evers, 2013]. During inflammation, enzymes such as CYP450 can be down-regulated leading to instances of reduced clearance and increased plasma concentrations of administered drugs. The administration of GSK3196165 can potentially alter circulating cytokine levels to a patient whose cytokine levels have been elevated. This may partially or completely reverse the impact of cytokines on CYP450 enzymes leading to changes in the exposure of co-administered drugs whose metabolism is dependent on CYP450 enzymes. The reports so far suggest the magnitude of drug interaction by therapeutic proteins (clinically) is generally small (less than two-fold) and therefore only likely to be clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of GSK3196165, in subjects being treated with these types of medicinal products, therapeutic monitoring of effect (*e.g.*, warfarin) or drug concentration (*e.g.* theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when GSK3196165 is co administered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, *e.g.*, oral contraceptives, lovastatin, atorvastatin, *etc*. The effect of GSK3196165 on CYP450 enzyme activity may persist for several weeks after stopping therapy.

6.11.1. Permitted Medications and Non-Drug Therapies

All permitted medications and non-drug therapies will be recorded as concomitant medications.

6.11.1.1. Corticosteroids

6.11.1.1.1. Oral Corticosteroids

Stable use of oral corticosteroids ≤10 mg/day prednisone or equivalent agent is permitted if the dose is stable for at least 28 days prior to Day 1 (baseline). This dose should remain constant throughout the first 12 weeks of the study. Dose reductions before Week 12 are not permitted, unless required for safety or tolerability.

If the corticosteroid dose is increased above 10 mg/day prednisone, the subject will be deemed a treatment failure and investigational product will be discontinued, although the subject will remain on study and undergo study visits as outlined in the Time and Event Table Section 7.1.

6.11.1.1.2. NSAIDS

Continued use of single NSAID (including Cox-2 inhibitors) is permitted (*i.e.* diclofenac, ibuprofen, naproxen, celecoxib) in daily doses up to the maximum recommended dose, according to locally accepted clinical practices, if the dosage was stable for at least 14 days prior Day 1. The dose/type of NSAID may be changed for safety or tolerability problems. If the subject is not regularly using NSAIDs, he/she may take the NSAIDs mentioned above as breakthrough pain management, which must be recorded in the eCRF. However, subjects should be advised not to take any NSAIDs for breakthrough pain within 12 hours prior to an efficacy assessment visit.

6.11.1.2. Analgesics

Regular use of codeine, opium alkaloid, paracetamol/acetaminophen, propoxyphene, and tramadol are permitted in daily doses up to the maximum recommended according to locally accepted clinical practices. If the subject is not regularly using any analgesics, he/she may take the analgesics mentioned above as breakthrough pain management. However, the subjects should be advised not to take any analgesics for breakthrough pain within 12 hours prior to an efficacy assessment visit.

6.11.2. DMARD/Biologic Rescue Medications

The subject's disease will be assessed regularly throughout the study (as shown in Section 7.1). Subjects (other than those on the 180 mg dose) will be escalated to the 180 mg (or highest remaining) dose of GSK3196165 at Week 12 if they fail to achieve a EULAR good/moderate response, or at Week 24 if their DAS28(CRP) score is above 3.2. Every effort should be made to keep the subject on study treatment unless the subject experiences an excessive disease flare that, in the investigator's opinion, warrants a change in therapy.

6.11.3. Prohibited Medications and Non-Drug Therapies

6.11.3.1. Related to the Study

- Any conventional DMARDs other than MTX (including hydroxychloroquine, leflunomide, sulphasalazine, minocycline, ciclosporin, azathioprine).
- Any biologic agent (such as TNF inhibitors such as adalimumab, etanercept, infliximab, certolizumab pegol, golimumab or non-TNF inhibitors (including abatacept, rituximab, tocilizumab and belimumab) and any anti-rheumatic investigational compounds.
- IA corticosteroids are strongly discouraged within 8 weeks prior to Day 1, and then through Week 52.
    - However, IA corticosteroids may be used in a limited fashion as treatment for severe RA flares.
    - No more than 1 joint per 24-week period or 2 joints per 52-week period should be injected.
    - No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of IA corticosteroid should not exceed 80 mg of triamcinolone (or equivalent) during the 52-week period.
- IV and/or IM steroids are not permitted for at least 28 days prior to Day 1, or throughout the study.
- Live vaccines should not be administered for 12 weeks after the last dose of GSK3196165. Furthermore, GSK3196165 and MTX are immunosuppressive and may therefore reduce immunological response to concurrent vaccination. In addition, investigators are expected to assess vaccination status, including against influenza and pneumococcus according to local guidelines.

6.11.3.2. Related to Methotrexate

Refer to local prescribing information for warnings, precautions and contraindications with MTX treatment.

- Prohibited:
    - Concomitant administration of folate antagonists such as trimethoprim, cotrimoxazole and nitrous oxide are prohibited.
    - Vitamin preparations containing folic acid or its derivatives may alter response to MTX (although folic acid is recommended to reduce the side-effects of MTX, it must not be administered on the same day as MTX)
- Caution advised with the following:
    - MTX is extensively protein bound and may displace, or be displaced by, other acidic drugs. The concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, penicillins, ciprofloxacin, diphenylhydantoins, phenytoin, acidic anti-inflammatory agents, salicylates,

sulphonamides, tetracyclines, thiazide diuretics, probenicid or sulfinpyrazone or oral hypoglycemics will decrease the MTX transport function of renal tubules, thereby reducing excretion and may increase MTX toxicity.

- MTX may also interact with mercaptopurine and theophylline. Acitretin (a treatment for psoriasis) is metabolised to eretinate. MTX levels may be increased by eretinate and severe hepatitis has been reported following concomitant use.
- Concomitant use of aspirin or NSAIDs
- Hepatotoxic and nephrotoxic drugs.

6.11.3.3. Complementary Therapies

The use of complementary therapies that may affect RA disease activity or assessments, including, but not limited to, traditional medicine (*e.g.* Chinese, acupuncture, Ayurvedic) is prohibited.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1).

7.1. Time and Events Table (Combination Treatment with GSK3196165 and MTX)

Procedures	Screening - up to 4 weeks		Baseline	Treatment Period																																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			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	Day	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	
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]

Procedures	Screening - up to 4 weeks		Baseline	Treatment Period																																				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			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	Day	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	
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
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	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	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	X
Urinalysis (dip stick)	X							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	U
TB, HBsAg, Hep B cAb, HepC Ab, HIV	X																																						
RF, ACPA (anti-CCP)	X																																						
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

Procedures	**Screening - up to 4 weeks**		**Baseline**	**Treatment Period**																																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			**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	**Day**	**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	
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											

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 (see Section 7.6) 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.

7.2. Screening and Critical Baseline Assessments

After written, informed consent (including separate consent for genetics research and actigraphy sub-study at participating sites), screening assessments will be performed. Screening procedures are outlined in the Time and Events Table (Section 7.1). All screening assessments must be performed within 28 days of Day 1 (except for subjects being treated with azathioprine or leflunomide, where written informed consent for the study, or sub-study, must be obtained prior to beginning the screening period). Women and men of reproductive potential must consent to use of a highly effective method of contraception for the duration of the study and for 12 weeks after study end (see Appendix 12.2), and the method (s) used by each subject must be documented.

- The following demographic parameters will be captured: year of birth, sex, race and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.
- Rheumatoid arthritis history – disease duration, medication history, RA functional class (I, II or III).
- Physical examination (complete examination at screening, and brief examination at Day 1 visit; see Section 7.4.8).
- Vital signs including temperature, sitting blood pressure, and heart rate.
- Triplicate 12-lead ECG (before blood samples are taken).
    - Spirometry FEV1, FVC and D_{LCO} (see SRM for additional details).
- Blood samples for:
    - Hematology (full/complete blood count and differential), including ESR (screening and baseline).
    - Biochemistry (screening and baseline).
    - Serum βhCG pregnancy test (screening).
    - HIV antibody, Hepatitis B surface antigen, anti-HBc, and Hepatitis C antibody testing (screening).
    - CRP (screening and baseline).
    - Autoimmune serology: RF and ACPA (*i.e.*, anti-CCP antibodies) (screening).
    - QuantiFERON Gold or T-spot test for TB (If unavailable/unapproved, then tuberculin skin test is permitted). TB tests may be performed locally.
    - Exploratory GM-CSF, PD and lung biomarkers (baseline).
    - Plasma PK samples and immunogenicity (baseline).
    - Pharmacogenomic and RNA transcriptomic tests (in consenting subjects).

- Urine sample for:
  - Routine urinalysis (screening).
  - Urine βhCG pregnancy test (baseline).
- Disease activity assessments (screening and baseline) (see Section 7.3)
  - Tender joint count (68 joints).
  - Swollen joint count (66 joints).
  - Patient's Assessment of Arthritis Pain.
  - Patient's Global Assessment of Arthritis.
  - Physician's Global Assessment of Arthritis.
  - HAQ-DI.
- Patient-reported outcome questionnaires (baseline) (see Section 7.10)
  - Component of BFI.
  - FACIT-Fatigue.
  - Acute SF-36.
  - RA Symptom and Impact Diary.
  - Actigraphy (in consenting subjects at participating sites).

Patient-reported outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified in the SRM.

7.3. Efficacy

Efficacy assessments will be performed at the time points presented in the Time and Events Table (Section 7.1).

Efficacy assessments will include evaluation of all 68 joints for tenderness and 66 joints for swelling to be performed by an independent joint evaluator, VAS (global disease) for the subject and treating physician, health assessment questionnaire – disability index (HAQ-DI – physical function, which includes an item on pain severity in the past week), as well as other Health outcome measures described in more detail in Section 7.10 and laboratory assessments (CRP). Based on these assessments ACR (20, 50 and 70), DAS28(CRP) and the EULAR response will be calculated.

For those subjects in the actigraphy sub-study at participating sites, physical activity levels will be assessed using actigraphy/an accelerometer. RA symptoms will be assessed through the subject completion of a daily RA Symptom and Impact Diary (see Section 7.10).

7.3.1. Joint assessments

The procedure for joint assessments can be found in the SRM.

7.3.1.1. Replaced or Fused Joints

Replaced or fused joint will not be included in joint evaluations. The reason for absence of the evaluations of those joints must be recorded.

7.3.1.2. Independent Joint Evaluator

One or more independent assessors, who have documented experience in performing joint assessments, will be designated at each trial site to perform joint assessments. Preferably the same independent assessor will perform all joint assessment for the same subject throughout the trial. The principal investigator must ensure that the independent joint assessor has documented experience and he/she is adhering to locally accepted and implemented standards. This also applies if the independent joint assessor is replaced during the trial.

The independent joint assessor should have no other contact with the subject during the trial, must not be the treating physician (investigator), should not discuss the subject's clinical status with the subject during the joint assessment nor with other site personnel, and will not be permitted to review the subject's medical records, the eCRF, nor any of the previous joint assessments.

7.3.2. Patient's Assessment of Arthritis Pain

Subjects will assess the severity of their current arthritis pain using a 100 unit visual analog scale (VAS) by placing a mark on the scale between "0" (no pain) and "100" (most severe pain), which corresponds to the magnitude of their pain.

Further details of this assessment are provided in the SRM.

7.3.3. Patient's Global Assessment of Arthritis

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

Further details of this assessment are provided in the SRM.

7.3.4. Physician's Global Assessment of Arthritis

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

Further details of this assessment are provided in the SRM.

7.3.5. DAS Assessments

The Disease Activity Score (DAS) assessment is a derived measurement with differential weighting given to each component. The DAS 28(CRP) or DAS 28(ESR) will be calculated at each assessment timepoint.

The components of the DAS 28 arthritis assessment include:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- CRP or ESR.
- Patient's Global Assessment of Arthritis.

Sites/investigators will not have access to ongoing DAS scores, apart from the screening and Day 1 results (needed to confirm eligibility). DAS28(ESR) value on Day 1 will be used to confirm disease activity eligibility by the IRTS before dosing.

7.3.6. ACR Assessments

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvement. This efficacy measurement will be made at every study assessment timepoint.

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

- Tender/Painful Joint count (68).
- Swollen Joint Count (66).
- Patient's Assessment of Arthritis Pain.
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.
- CRP or ESR.
- Health Assessment Questionnaire – Disability Index (HAQ-DI).

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

7.4.1. Screening visit(s)

- Chest X-ray (PA and lateral, or in accordance with local requirements).
    - if a chest X-ray has been taken within the past 12 weeks that shows no clinically-significant abnormality, and there are no signs or symptoms suggestive of pulmonary disease that would exclude the subject, then a further chest X-ray is not required.

- Baseline chest HRCT for subjects with D_{LCO} values ≥60% to <70%, and it is recommended that the subject will be reviewed by a local pulmonologist to exclude significant pre-existing respiratory disease.
- Immunogenicity testing.

7.4.2. Study visits

Subjects will have systematic safety monitoring throughout the study. Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

In addition to routine laboratory assessments, ECG monitoring, and evaluation of adverse events, particular attention will be paid to respiratory events and function given the potential risk associated with targeting GM-CSF and the effects on alveolar macrophages. This may result in the occurrence of the extremely rare condition of PAP, which is characterized by the accumulation of surfactant lipids and protein in the alveolar spaces (with no fibrosis), with resultant impairment in gas exchange, which may lead to increase a risk of secondary pulmonary infections.

All subjects will return for a follow-up visit at 12 weeks after last dose of study medication.

7.4.3. Safety endpoints and other assessments

- Incidence of AEs/SAEs.
- Incidence of serious infections and opportunistic infections.
    - Pulmonary events (cough, dyspnea, pulse oximetry, spirometry, D_{LCO}).
- Lung biomarkers (such as SP-D, KL-6, LDH, cholestenoic acid).
- ECG measurements.
- Vital signs.
- Hematological and clinical chemistry parameters.
- Physical examinations.
- Pregnancy test (for women of child-bearing potential).

7.4.4. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 12.4.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.4.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (12 weeks after the last dose of investigational product), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (*e.g.*, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 12.4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 12.4.

7.4.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.7.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 12.4.

7.4.4.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 12.4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF

will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

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

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

7.4.5. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (*e.g.*, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

7.4.6. AEs of Special Interest

Please see Section 4.7.1 for a discussion of potential risks with GSK3196165. Adverse events of special interest include:

- Serious infections, including serious respiratory infections.

- Opportunistic infections including TB reactivation.
- Neutropenia.
- Non life-threatening pulmonary changes related to surfactant accumulation.
- PAP.
- Hypersensitivity reactions, including anaphylaxis.
- Injection site reactions.
- Persistent cough or dyspnea.

7.4.6.1. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following have been specified as disease-related events (DREs) for the study:

- Events related to exacerbation of articular/peri-articular manifestations of RA, will not be reported as AEs, and will be recorded in the DRE eCRF.
- Events related to the articular/peri-articular flare up of the disease, and that require hospitalization, will not be reported as SAEs. However, such events must still be recorded in the DRE eCRF.

These DREs will be monitored by an SRT on a routine basis.

NOTE: However, if either of the following conditions apply, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject.

OR

- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.

New onset or worsening of extra-articular manifestations of RA should be reported as AEs/SAEs.

7.4.6.2. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (*e.g.*, summary or listing of SAEs) from GSK will file it with the IB GSK Document Number [2014N190256_01] and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.7. Pregnancy

Any pregnancy (participating females and female partners of participating males) that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence and should follow the procedures outlined in Appendix 12.5.

7.4.8. Physical Exams

- A complete physical examination at the Screening visit will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination at subsequent assessments will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.4.9. Vital Signs

- Vital signs will be performed prior to dosing with GSK3196165.
- Vital signs will be collected as indicated in the Time and Event Table (Section 7.1).
- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.
- A single set of values will be collected and recorded in the source documentation and eCRF.

7.4.10. Electrocardiogram (ECG)

See Section 5.2 regarding QTc exclusion criteria.

- Triplicate 12-lead ECGs will be obtained (before dosing and blood samples taken) at the time points presented in the Time and Events Table (Section 7.1) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary. ECGs will also be transferred and read centrally.

7.4.11. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7.1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Central Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (*e.g.*, SAE or AE or dose modification) the results must be recorded in the eCRF.

Refer to the central laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- ESR
- The results of each test must be entered into the eCRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the eCRF.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 2.

Table 2 Routine 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 sediment for erythrocytes, leukocytes and casts if urine dipstick abnormal
Erythrocyte count	Creatinine clearance (calculated)	
Reticulocyte count	Aspartate transaminase (AST)	
Leukocyte count	Alanine transaminase (ALT)	
Leukocyte differential count	γ-glutamyl transpeptidase	
neutrophils		
eosinophils		

Hematology	Biochemistry	Urinalysis
basophils monocytes lymphocytes Platelets Activated partial thromboplastin time (aPTT) Prothrombin Time (PT) International Normalised Ratio (INR) Fibrinogen Erythrocyte Sedimentation Rate (ESR)*	(GGT) Lactate dehydrogenase (LDH) Alkaline phosphatase (AP) Bilirubin (total) Creatine Phosphokinase (CPK) Total protein Albumin Albumin/globulin ratio Serum Glucose C-reactive protein (CRP) Cholesterol** Triglycerides** High-density lipoprotein (HDL)** Low-density lipoprotein (LDL)**	Urine pregnancy test

*Measured locally

**Fasting tests

All laboratory tests with values that are considered clinically-significantly abnormal during participation in the study or within 12 weeks after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Serum will be collected at baseline and throughout the study to measure potential biomarkers of lung damage such as SP-D, KL-6, LDH, and cholestenoic acid (see Section 7.7). Baseline measurement of GM-CSF autoantibodies will be measured.

7.4.12. Pulmonary Assessments

Pulmonary assessments are a key aspect of the safety monitoring in this study.

The following pulmonary assessments will be performed at the time points presented in the Time and Events Table (Section 7.1).

- Chest X-ray.
- Cough.
- Borg dyspnea questionnaire.
- Lung auscultation.
- Pulse oximetry.
- Pulmonary function tests (PFTs - spirometry, gas transfer [D_{LCO}]).

PFT assessments will be standardized across study sites by the vendor.

In the event of any new or clinically significant pulmonary abnormalities that may develop during the study (*e.g.*, increased shortness of breath/dyspnea, or unexplained and persistent coughing; or >15% relative decrease in D_{LCO} from baseline), it is recommended that the subject be referred to a pulmonologist for further assessment. The study drug should be suspended until the symptoms or signs that caused referral have resolved and/or the underlying diagnosis has been determined and clinically significant events have been excluded by the pulmonologist. Suggested pulmonary assessment/management algorithms are provided in a separate Pulmonary Safety Guidance Document in the SRM.

Additional pulmonary imaging (HRCT) or other tests may be performed on a subject during the study to investigate pulmonary abnormalities, and the DRC or SRT may request copies of any reports or images for central review.

7.5. Pharmacokinetics

Blood samples for pharmacokinetic analysis of GSK3196165 will be collected at the time points indicated in the Time and Events Table (Section 7.1). The actual date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Details of PK blood sample collection, processing, storage and shipping procedures are provided in the central laboratory manual.

7.5.1. Sample analysis

Sample analysis will be performed under the control of GSK. Concentrations of GSK3196165 will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

PK analyses are described in Section 9.4.4.

7.6. Immunogenicity

GSK3196165 is a humanized monoclonal antibody that will be delivered by the subcutaneous route and is targeted to bind and neutralize a soluble target, and for these reasons, is considered to be a relatively low risk of inducing adverse immune responses [FDA, 2014].

Serum samples will be collected and tested for presence of antibodies that bind to GSK3196165. Serum samples for testing anti-GSK3196165 antibodies will be collected as described in the Time and Events schedule (Section 7.1). The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Central Laboratory Manual.

The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly-available data to ensure appropriate safety monitoring. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing, at the time of the event and again 12 weeks after. For subjects who prematurely withdraw from the study, immunogenicity testing will occur at withdrawal and at follow-up 12 weeks after last dose.

Serum will be tested for the presence of anti-GSK3196165 antibodies using the currently approved analytical methodology using a tiered testing schema: screening, confirmation and titration steps. The presence of treatment emergent anti-drug antibodies (ADA) will be determined using a GSK3196165 bridging style ADA assay with a bio-analytically determined cut point determined during assay validation. Samples taken after dosing with GSK3196165 that have a value at or above the cut-point will be considered treatment-emergent ADA-positive. These ADA positive samples will be further evaluated in a confirmatory assay, and confirmed positive samples will be further characterized by assessment of titer. Results of anti-GSK3196165 antibody testing will be reported at the end of the study and will include incidence and titer. The presence or absence of antibodies to GSK3196165 in dosed subjects will be analyzed, then summarized descriptively and/or graphically presented.

7.7. Biomarker(s)/Pharmacodynamic Markers

With the subject's consent, blood samples will be collected at the time points indicated in the Time and Events Table (Section 7.1) to investigate pharmacodynamic response to GSK3196165 and will be analysed pre- and post-GSK3196165. In addition blood samples will be collected and may be analysed for markers which may be predictive of lung damage and changes in CYP3A4 activity. The timing of the collections may be adjusted on the basis of emerging PK, pharmacodynamic or safety data from this study or other new information in order to ensure optimal evaluation of the pharmacodynamic endpoints. Details on the blood sample collection, processing, storage and shipping procedures are provided in the Central Laboratory Manual. All samples may be retained for a maximum of 15 years after the last subject completes the study. Results of biomarker studies may be reported separately from the main clinical study report, and additional exploratory analyses may be performed to further characterize novel biomarkers.

Target engagement with soluble GM-CSF will be assessed. Serum will be collected to measure concentrations of free soluble GM-CSF and soluble GM-CSF complexed to GSK3196165 and correlated to PK.

A broad range of markers in serum collected at various timepoints as outlined in the Time and Events Table (Section 7.1) may be measured in serum including, but not limited, to:

- Safety biomarkers which may be predictive of lung damage including, but not limited to, the following:

- Analysis of SP-D, KL-6, cholestenoic acid, LDH and measurement of GM-CSF autoantibodies at baseline.
- These will be analysed at the end of the study or in the event of a pulmonary safety signal which would require further investigation.

Therapeutic proteins, such as GSK3196165, have the potential to reverse the suppression of cytochrome P450 expression levels. To investigate this endogenous 4β-hydroxycholesterol, a metabolite of cholesterol previously reported to be a clinical biomarker of CYP3A enzyme activity will be monitored [Nylén, 2011]. Since the cholesterol levels are expected to fluctuate throughout the study, the ratio of 4β-hydroxycholesterol to cholesterol, instead of 4β-hydroxycholesterol alone, will be explored as a potential biomarker of CYP3A activity in this study. Biomarkers predictive of a change in CYP3A4 activity may include, but not limited to, the following:

- Plasma analysis of cholesterol/4β-hydroxycholesterol ratio

Pharmacodynamic biomarkers may include, but not limited to, the following:

- Target engagement: analysis of free soluble GM-CSF and soluble GM-CSF complexed to GSK3196165.
- Soluble biomarkers which may be predictive of response to GSK3196165 such as MRP8/14, CCL17 (TARC), ARGS, MMP-3, YKL-40, SAA and 14-3-3η.
- Serum cytokines to monitor mechanism of action of GSK3196165 such as IL-6, IL-1β, TNFα, IL-17A, IL-17F, CCL17/Thymus and activation regulated cytokine (TARC).
- Additional cytokines on a Mesoscale discovery (MSD) multiplex panel will include measurement of IL-8, IL-4, IL-10, IL-13, and IFNγ.

Additional exploratory biomarkers in the blood/serum (RNA, DNA, protein) may include but will not be limited to the following:

- Serum analysis (*e.g.*, MMP-3, YKL-40, SAA, IL-23, *etc*.).
- RNA analysis of blood.

7.8. Novel Biomarkers

With the subject's consent, blood sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence RA, and/or medically related conditions, as well as the biological and clinical responses to GSK3196165. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Evaluation of a range of exploratory novel biomarkers will allow confirmation of target engagement and expected pharmacologic effects. These data may also allow hypotheses to be generated with respect to subgroups that are most likely to benefit from GSK3196165 treatment or early on-treatment biomarkers that may predict subsequent response/remission (or lack of response/remission), that may guide Phase III development and ultimately treatment guidelines for prescribers.

Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome and samples may be selected for analysis on the basis of the clinical outcome. Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK3196165 is observed.

Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK3196165 or provide new insights into RA and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of GSK3196165. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

Details on the blood sample collection, processing, storage and shipping procedures are provided in the Central Laboratory Manual.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with RA or medically related conditions and/or the action of GSK3196165 may be identified by application of:

- RNA transcriptome analysis of blood samples.
- Measurement of the levels of a subset of RNA species on blood samples.

7.9. Genetics

Information regarding genetic research is included in Appendix 12.6.

7.10. Value Evidence and Outcomes

Planned timepoints for all health outcomes assessments are presented in the Time and Events Table (Section 7.1), and further details of all assessments are provided in the SRM.

7.10.1. Health Assessment Questionnaire – Disability Index (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 [Fries, 1980]:

- dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities.

7.10.2. Brief Fatigue Inventory (BFI)

The purpose of the BFI is to assess the severity of fatigue and the impact of fatigue on daily functioning. This self-reported instrument consists 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.

7.10.3. FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) -fatigue questionnaire is a patient-reported measure developed originally to assess fatigue in individuals with cancer validated. The FACIT-fatigue has subsequently been used and validated in numerous chronic conditions, including RA.

7.10.4. SF-36 Short Form Health Survey

Health-related quality of life (HRQL) will be assessed using the subject-completed Medical Outcomes Study (MOS) 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.

7.10.5. RA Symptom and Impact Diary PRO

Symptoms associated with RA will be assessed using a novel RA Symptom and Impact Diary. Subjects participating in the actigraphy sub-study at participating sites will complete the RA Symptom and Impact Diary on a daily basis, at home, during the periods when the actigraphy device is placed on their person. All other subjects will complete the RA Symptom and Impact Diary PRO during a study visit at 12-weekly intervals, as per the Time and Events Schedule (Section 7.1).

7.10.6. Exploratory Health Outcomes Assessment - Actigraphy

Actigraphy is a non-invasive method of measuring rest and activity cycles. Daily activity and walking can be measured over time using motion-sensing devices, such as accelerometers, which measure positional change and motion. Actigraphy has been used as a tool to assess daily activity of subjects with impaired mobility [Reiterer, 2008], and may be particularly appropriate as the majority of RA patients present with arthritis of the feet and 20% of them have radiographic damage at the time of diagnosis [Michelson, 1994]. Sleep deficit associated with RA and fatigue associated with osteoarthritis (OA) have also previously been investigated using actigraphy [Clarke, 2013; Murphy, 2013]. The development of a tool which "objectively" measures RA subjects' degree of gross mobility and activity could provide useful novel endpoints for demonstrating treatment-associated improvement of RA symptoms including fatigue, morning stiffness and joint inflammation.

In this study, actigraphy data will be captured for a subset of consenting subjects at participating sites by a commercially available, continuous logging, three-axis electronic accelerometer. Actigraphy data will be collected throughout the study as described in the Time and Events Table (Section 7.1). Exploratory actigraphy endpoints may be evaluated as change from baseline and change over time. The accelerometer will be placed on the subject upon visiting the clinic (asked to perform a short set of specific physical exercises) and will be worn by the subject continuously for up to 14 days of data collection. At the end of the data collection period, coinciding with a study visit, the accelerometer will be removed, the raw data downloaded, and the unit cleaned and

recharged for reuse. The raw accelerometer data will be analysed using an RA-specific algorithm being developed by GSK. At present, the algorithms are exploratory and un-validated. The processed data will be sent to GSK for final statistical analysis. The subject's activity/lifestyle, residence and working status during the data collection period will be recorded in the eCRF. The date and time of sensor placement and removal will also be recorded in the eCRF.

This study will aim to explore the application of actigraphy by:

1. Measuring quantitative measures of physical activity and sleep in RA patients.
2. Evaluating treatment effects of GSK3196165 on physical activity and sleep in RA patients.
3. Evaluating how measures of physical activity relate to subject reported measures of symptoms and other efficacy assessments including DAS28(CRP), ACR and biomarkers of disease activity.

Measures to include but may not be limited to:

1. Daily and intra-daily physical activity to include time spent walking, time spent standing, time spent lying down, time spent sitting. Other measures may be derived from these data including overall time spend active, overall time spent sedentary, total Activity Score (amount and intensity of activity), duration of morning stiffness and number of continuous walking periods above a predefined threshold.
2. Sleep quality – to include time spent lying, number of movement episodes, sleep efficiency (function of % of movement time and % of lying time) and fragmentation index (function of movement time % and number of movement episodes).

The results from these assessments will be reported separately.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK-defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses

The primary endpoint of the study is to evaluate the proportion of subjects that achieve DAS28(CRP) remission (DAS28 <2.6) following 24 weeks of treatment with GSK3196165 or matching placebo in adult subjects on concomitant MTX therapy.

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 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.

The null hypothesis (H0) for the dose response relationships assumes that there is no effect of the test drug and hence no evidence of dose-response. This is equivalent to saying that none of the doses are superior to 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. The details of how the dose-response model will be described are outlined in Section 9.4.2.

The alternative hypotheses to be tested are as follows:

DAS28(CRP) Change from Baseline: H1: Placebo ≥22.5 mg ≥45 mg ≥90 mg ≥135 mg ≥180 mg

9.2. Study Design Considerations

9.2.1. Sample Size Assumptions

The sample size assumptions outlined below for the primary and key secondary objectives 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:

9.2.1.1. 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 α=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 a 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.

9.2.1.2. 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.

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 3 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.

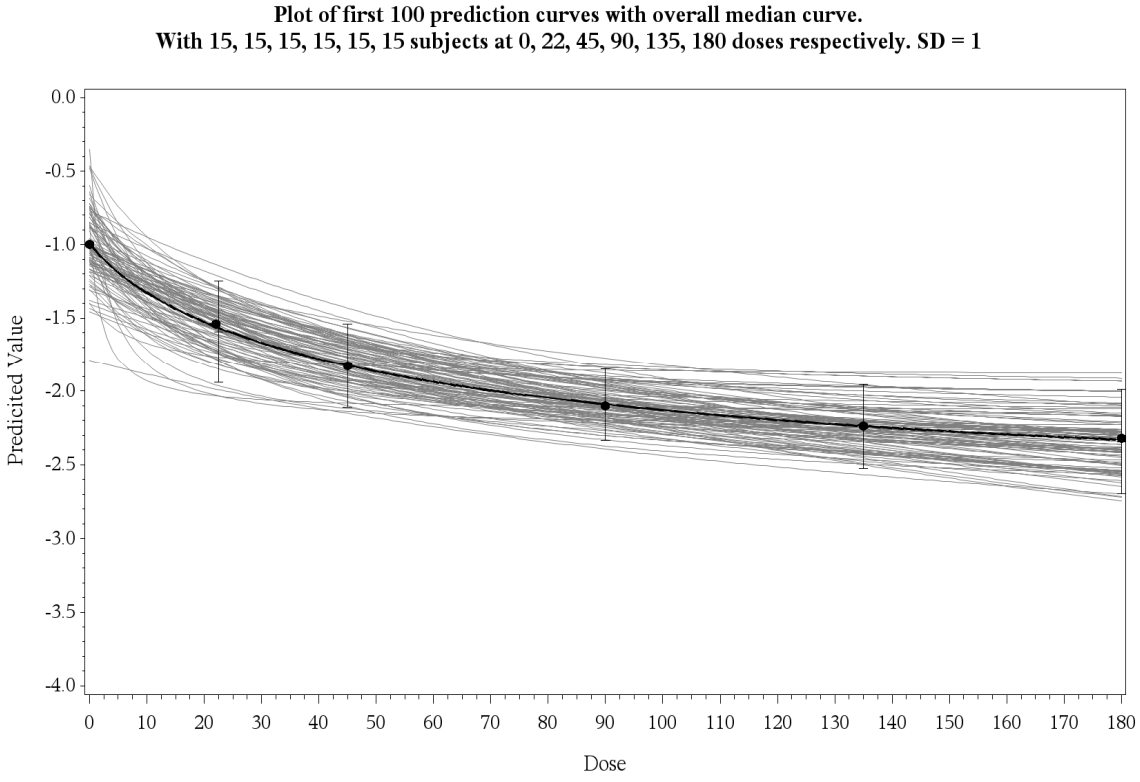
Figure 2 shows the first 100 prediction curves (from 100000 simulations) and the overall median curve with the assumptions outlined above, illustrating the anticipated dose response curve with 15 subjects per arm. The black vertical intervals around each dose represent the change from baseline in DAS28(CRP) that are the 2.5 and 97.5 percentile values from all simulations.

Table 4 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 4 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%

Figure 2 Plot of the First 100 Prediction Curves with the Overall Median Curve at the Dose Response Analysis



9.2.2. Sample Size Sensitivity

9.2.2.1. Primary Analysis

The power of the study will be affected by changes from the assumed remission rate and Table 5 shows the effect on power under varying remission rates on both MTX and GSK3196165 assuming a fixed sample size of 35 per arm.

Table 5 Power for Remission Endpoint 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%

9.2.2.2. 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)). Table 6 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.

Table 6 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	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 7 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 7 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

9.2.3. Sample Size Re-estimation

No sample size re-estimation is planned, though the maximum sample size per group may be higher than 35 subjects depending on any decisions to change the randomisation. The maximum sample size of the study will not be increased.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent to Treat (ITT) population: The ITT population is defined as all subjects who were randomised to treatment and who received at least one dose of study treatment.

Pharmacokinetic (PK) population: The PK population is defined as all subjects who were randomised to treatment, who received at least one dose of study treatment and who have at least one valid pharmacokinetic assessment.

9.3.2. Analysis Data Sets

For the binary endpoints (*e.g.* proportion of subjects achieving remission at 24 weeks), subjects with missing efficacy data (caused by prematurely discontinued subjects or otherwise) or subjects who received rescue treatment will be imputed as non-responders. A dataset will be created with this imputation and will be referred to as Non-Responder Imputation (NRI) and will be the primary dataset used for all binary endpoints.

In addition to the Non-Responder Imputation dataset for binary endpoints, for all efficacy endpoints a Observed Case (OC) dataset will be created, whereby the data are as collected or observed in the study and no imputation is made for missing data. All continuous endpoints will be analysed using the OC dataset and all data will be listed using the (OC) dataset.

9.3.3. Interim Analyses

Interim analyses will be conducted to assess the efficacy or futility of GSK3196165 in this study. Recruitment will continue while the interim analyses are being conducted.

The interim analyses to assess futility and possible adaptation of doses will be performed when appropriate data are available and full details will be provided in a separate guidance document for the data review committee and the analysis plan which will be available prior to the data being unblinded. To prevent potential unblinding of the

investigator and potential bias to the study, details of the timing of the interim analysis, data to be reviewed and the interim analysis decision rules are not being provided in the protocol.

The specific guidance around the decision to stop further randomisation will be specified in the review group guidance document and will be agreed with the review group members prior to the first data review.

Safety data will also be reviewed on an on-going basis as defined in Section 4.3 and Section 10.8.1.

In addition, the interim analysis may also allow an assessment of subjects with early RA (<2 years disease duration), and, based on results, the proportion of subjects in this subgroup required to be randomised may be revised.

9.4. Key Elements of Analysis Plan

Full details of all analyses will be provided in the analysis plan.

9.4.1. Primary Analyses

The primary efficacy endpoint is the proportion of subjects achieving DAS28(CRP) remission at Week 24 of the 52-week double-blind treatment period in the ITT population using NRI. DAS28(CRP) remission is defined as a DAS28 score of <2.6 points. The DAS28(CRP) score is calculated using the following formula, where TJC = tender joint count, SJC = swollen joint count and PtGA = Patient's Global Assessment of Arthritis:

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

Subjects with missing DAS28(CRP) scores at Week 24 will be considered as non-remitters. The proportion of subjects in DAS28(CRP) remission will be summarised using counts and proportions in remission and analyzed using a logistic regression analysis adjusted for treatment group and baseline DAS28(CRP) score and will be used to test the treatment comparison of each GSK3196165 dose group versus placebo. For each treatment comparison, an estimate of the odds ratio of achieving remission and the corresponding p-value and 95% confidence interval will be summarised.

9.4.2. Secondary Analyses

The key secondary analysis of assessing dose response at 12 weeks will be based on the change from baseline in the DAS28(CRP) continuous score after 12 weeks of treatment. Primary inference will be based on the ITT population, as defined in Section 9.3.1 and the analysis will be performed using the OC dataset. Further sensitivity analyses using multiple imputation may be conducted if the rate of dropout is larger than expected (<10% to Week 12).

It is expected that the shape of the dose response curve will be sigmoidal and the data will be initially analyzed using a three parameter E_{max} model of the form:

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

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

If this E_{max} model is not applicable then additional models will be investigated, including a four parameter E_{max} model and the model with the expected response as a linear function of dose. These models will be detailed in the reporting and analysis plan (RAP), along with further details of the analyses to be conducted. Each of the models will be fitted to the data and their fit compared using the Aikake 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 underlying this analysis will be assessed (further details will be included in the RAP).

All binary secondary endpoints will be analyzed using the same methods as for the primary endpoint. Continuous secondary endpoints, apart from the assessment of dose response, will be analyzed using a repeated measures model (MMRM). Further sensitivity analyses may be conducted using multiple imputation if the rates of dropout are high. Full details will be given in the RAP.

9.4.3. Other Analyses

All safety evaluations will be based on the ITT population. Clinical interpretation will be based upon review and displays of extent of exposure, adverse events (AE), serious adverse events (SAEs) and AEs of Special Interest, premature discontinuations, laboratory values, vital signs, and changes in pulmonary function (*e.g.*, spirometry, D_{LCO}). Analyses of AEs by the investigator-reported relationship to investigational product will also be performed.

Full details of all summaries and analyses will be included in the RAP.

Safety data will be monitored throughout the study and key events will be analysed using Bayesian methods. Full details will be provided in the DRC Charter and guidance document.

9.4.4. Pharmacokinetic Analyses

PK analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, GlaxoSmithKline. Concentrations of GSK3196165 and MTX in serum will be listed and summarised by treatment group and nominal time. Standard summary statistics will be calculated (*i.e.* mean, standard deviation, median, minimum

and maximum). Individual serum concentration-time profiles and median/mean profiles by treatment group will be plotted.

Serum concentration levels of GSK3196165 from this study will be evaluated using a population pharmacokinetics model developed based on previous GSK3196165 data from healthy subjects (Phase I) and RA subjects from the Phase 1b study. Primarily, the model buildings will be conducted with aid of NONMEM VII. Other computing programs, *e.g*. MONOLIX, may also be used for model investigations. The aim(s) of this modelling approach will include:

- Define the population and individual systemic exposure ($AUC_{0\text{-}t,ss}$, $C_{max,ss}$, $C_{min,ss}$), volume distribution and clearance of GSK3196165 and the associated between- and within-subject variability.
- Explore the effects of subjects' characteristics (such as gender, weight, height, disease status, baseline GM-CSF levels, *etc*.) as potential sources of inter-individual variability in drug exposure.
- The model predicted exposure of GSK3196165 for each individual randomised in the GSK3196165 groups will be used to assist further PK-PD relationships for biomarkers and/or clinical response if possible. Further details on the analysis will be described in the RAP.

PK parameters will be presented in graphical and/or tabular form and will be summarised descriptively. All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

9.4.4.1. Pharmacodynamic Analyses

All pharmacodynamic data will be summarised, graphically represented and listed appropriately. More details are included in the RAP.

9.4.4.2. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory plots will be presented for individual and/or pooled plasma GSK3196165 concentrations versus the DAS28 change from baseline. If data permit, potential association between systemic exposure of GSK3196165 and identified pharmacodynamic markers (*e.g.* CRP, MRP8/14) and efficacy endpoints (*e.g.* probability of achieving DAS28(CRP) remission or response) will be studied. If deemed necessary, statistical modelling, including linear and non-linear models will be investigated. All the modelling investigation will be exploratory and details will be provided in the RAP.

9.4.5. Immunogenicity Analysis

Details of the statistical analysis will be provided in the RAP.

9.4.6. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively

and/or graphically summarised as appropriate to the data. Additional exploratory analyses may be performed to further characterize the novel biomarker(s).

9.4.7. RNA Transcriptome Analysis

RNA transcriptome profile data will first be normalised to enable direct comparison of all data sets. Uninformative data (RNA species in all samples below detectable limits or levels unchanged across all samples under comparison) will be removed and multivariate statistical analyses will be performed on the remaining data to uncover intrinsic differences and similarities in the levels of RNAs between the different samples, and groups of samples. Statistical tools such as Principal Component Analysis, PLS-Discriminant Analysis, and ANOVA using either standard or customised software will be used for the profile analysis to assist identification of patterns/profiles which may associate with treatment outcome or RA and medically related conditions.

9.4.8. RNA Expression Analysis of a Subset of RNA Species

RNA expression profile data are first normalised to enable direct comparison of all data sets. After data reduction to remove uninformative data (RNAs whose levels are below levels of detection for all samples, and those whose levels are unchanged across all samples) the remaining data will be subject to a series of multivariate statistical analyses to uncover intrinsic differences and similarities in the levels of RNAs between the different samples. This will include application of statistical tools such as Principal Component Analysis, and ANOVA using standard analysis software as well as software packages customised for such profile analysis to assist identification of patterns/profiles which may associate with treatment outcome and/or RA.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable).
- Investigator reporting requirements (*e.g.* reporting of AEs/SAEs/protocol deviations to IRB/IEC).

GSK will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent(s) must be obtained for each subject prior to participation in the study or sub-studies.
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK or designee may conduct a quality assurance assessment and/or audit of the site records,

and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK or designee monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (*e.g.*, for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (*e.g.*, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.8. Review Committees

10.8.1. Data Review Committee (DRC)

- A DRC will be utilised in this study to ensure objective medical and/or statistical review of efficacy and/or safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study via review of unblinded study data.
- The 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. The decision to stop the study or randomisation to specific arms will be made by the DRC.

- The DRC members will review unblinded summary safety data, and if required will review anonymised individual data on request. Only the DRC statistician will be unblinded to individual subject treatment allocations.
- At the defined interim analysis time points the DRC will also review unblinded efficacy data. 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. The schedule of planned interim analyses and the analysis plan for DRC reviews will be described in the relevant guidance documents that will be approved prior to the first analysis, which will be available upon request.
- The DRC will remain in place for review of emerging unblinded safety data until all subjects have completed the safety follow-up visit (*i.e.*, 12 weeks after the last dose of study medication, Week 62 visit). The Week 24 efficacy and safety analyses (primary analysis) will be made available to the study team more broadly and to regulatory authorities as these data will support future clinical development plans.
- 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.

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12. APPENDICES

12.1. Appendix 12.1 - Abbreviations and Trademarks

°C	Degree Celsius
µg	Microgram
ACPA	Anti-cyclic citrullinated protein antibody
ACR	American College of Rheumatology
ACR20/50/70	20%/50%/70% improvement in tender and swollen joint counts and 20%/50%/70% improvement in 3 of the 5 ACR-core set measures
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse event
ALT	Alanine transaminase
AMD	Age-related macular degeneration
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
AUC0-∞	Area under plasma (serum) concentration-versus-time curve (time zero to infinity)
AUC0-t	Area under the plasma (serum) concentration-versus-time curve (time zero to time of last quantifiable concentration)
BAL	Bronchoalveolar lavage
βhCG	Beta-subunit human chorionic gonadotropin
BCG	Bacillus Calmette-Guérin
BFI	Brief Fatigue Inventory
BMI	Body mass index
BNP	B-type natriuretic peptide
CDAI	Clinical disease activity index
CD20	Cluster of differentiation antigen 20
CDC	Complement-dependent cytotoxicity
CIA	Collagen-induced arthritis
COX	Cyclo-oxygenase
CPK	Creatine phosphokinase
CRO	Contract Research Organization
CRP	C-reactive protein
CTC	Common terminology criteria
CYP	Cytochrome P
CXR	Chest X-ray (radiograph)
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 of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
DMARD	Disease modifying antirheumatic drugs

DRC	Data Review Committee
DRE	Disease-related event
ECG	Electrocardiogram
eCRF	Electronic case report form
EOW	Every other week
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
EW	Early withdrawal
FACIT	Functional assessment of chronic illness therapy
FEV1	Forced expiratory volume in one second
FRP	Females of reproductive potential
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GGH	Gamma-glutamyl transpeptidase
GM-CSF	Granulocyte-macrophage colony stimulating factor
GM-CSFRα	Granulocyte-macrophage colony stimulating factor receptor α chain
GSK	GlaxoSmithKline
h	Hour
HAQ-DI	Health Assessment Questionnaire Disability Index
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HRCT	High-resolution computed tomography
HRT	Hormone replacement therapy
HV	Healthy volunteer
IA	Intra-articular
IB	Investigator's brochure
IC50	The half maximal inhibitory concentration
ICH	International Conference on Harmonization
IFNγ	Interferon gamma
IL-1β	Interleukin 1 beta
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-10	Interleukin 10
IL-13	Interleukin 13
IL-17	Interleukin 17
IL-22	Interleukin 22
IL-23	Interleukin 23
IM	Intramuscular
IMP	Investigational medicinal product
INN	International non-proprietary name
INR	International normalized ratio
IP	Investigational product
IR	Inadequate response
IRTS	Interactive response technology system
ITT	Intent to Treat
IU	International units

IV	Intravenous
kDa	Kilodalton
kg	Kilogram
KL-6	Krebs von den Lungen-6
L	Litre
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Lung function test
mAb	Monoclonal antibody
MCV	Mean cell volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
MMP-3	Matrix metalloproteinase 3
MSD	Mesoscale discovery
MSDS	Material safety data sheet
MSS	Modified Sharp score
MTX	Methotrexate
n.a.	Not applicable
n.d.	Not determined
ng	Nanogram
NOEL	No observed effect level
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
PAP	Pulmonary alveolar proteinosis
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PFT	Pulmonary function test
PtGA	Patient's Global Assessment of Arthritis
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetics
pM	Picomolar
PT	Prothrombin Time
PTS-DMPK	Platform Technologies and Science - Drug Metabolism and Pharmacokinetics
RA	Rheumatoid arthritis
RAP	Reporting and analysis plan
RF	Rheumatoid factor
SC	Subcutaneous
SAA	Serum amyloid A
SAE	Serious adverse event
SDAI	Simple disease activity index
SJC	Swollen joint count

SF-36	Short form (36)
SOP	Standard operating procedure
SP-D	Surfactant D
SRM	Study Reference Manual
SRT	Safety Review Team
t½	Elimination half-life
TARC	Thymus and activation regulated cytokine
TB	*Mycobacterium tuberculosis*
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TNFα	Tumor necrosis factor alpha
TST	Tuberculin skin test
ULN	Upper limit of normal

Trademark Information

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NONMEM VII
SF-36v2

12.2. Appendix 12.2 - Contraception eligibility criteria for female and male subjects

12.2.1. Females

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotropin [βhCG] test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation.
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion.
  - Hysterectomy.
  - Documented bilateral oophorectomy.

- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle-stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed below in the **Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)** requirements from 30 days prior to the first dose of study medication and until 12 weeks after the last dose of study medication and completion of the follow-up visit. **If using hormonal contraceptives, including oral, injections, implants, and patches, a secondary method of contraception must be used.**

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (*e.g.* calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant.

- Intrauterine device or intrauterine system.
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011].
- Injectable progestogen [Hatcher, 2011].
- Contraceptive vaginal ring [Hatcher, 2011].
- Percutaneous contraceptive patches [Hatcher, 2011].
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. If using hormonal contraceptives, including oral, injections, implants, and patches, a secondary method of contraception must be used. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.2.2. Males

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 12 weeks after the last dose of study medication.

a. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview.

b. Male condom plus partner use of one of the contraceptive options below:

- Contraceptive subdermal implant.
- Intrauterine device or intrauterine system.
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011].
- Injectable progestogen [Hatcher, 2011].
- Contraceptive vaginal ring [Hatcher, 2011].
- Percutaneous contraceptive patches [Hatcher, 2011].

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Male subjects should not donate sperm during the course of the study and should follow local guidelines thereafter.

Reference:

Hatcher RA, Trussell J, Nelson AL, *et al*, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media; 2011: 50. Table 3-2.

12.3. Appendix 12.3 - Liver Safety Required Actions and Follow-up Assessments

Liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted. • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>**	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained less than 12 weeks after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN **and** bilirubin ≥2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver chemistry increased monitoring criteria with continued therapy

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

Reference:

James LP, Letzig L, Simpson PM, *et al*. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009;37:1779-84.

12.4. Appendix 12.4 - Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (*e.g.*, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • Signs and symptoms of RA disease activity, *e.g.* joint pain, swelling, erythema, warmth, and stiffness, or expected progression, should not be reported as AEs, unless in the investigator's opinion they are of greater intensity, frequency or duration than

expected for the individual subject.

- Medical or surgical procedure (*e.g.*, endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (*e.g.*, hospitalization for signs/symptoms of the disease under study, death due to progression of disease, *etc*).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (*e.g.* sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥3xULN and total bilirubin* ≥2xULN (>35% direct), **or** • ALT ≥3xULN and INR** >1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3xULN and total bilirubin ≥2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical Monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The Medical Monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome.
- Agranulocytosis/Severe Neutropenia.
- Anaphylaxis & Anaphylactoid Reactions.
- Hepatotoxicity.
- Acute Renal Failure.
- Seizure.

- Stevens Johnson syndrome/Toxic epidermal necrosis.

12.4.4. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina. • Congestive heart failure. • Arrhythmias. • Valvulopathy. • Pulmonary hypertension. • Cerebrovascular events/stroke and transient ischemic attack. • Peripheral arterial thromboembolism. • Deep venous thrombosis/pulmonary embolism. • Revascularization.

12.4.5. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (*e.g.*, hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.6. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the IB GSK Document Number [2014N190256_01] and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up

information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4.7. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator at the CRO.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (*e.g.*, InForm system) will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator at the CRO by telephone.
- Contacts for SAE receipt can be found in the SRM.

12.5. Appendix 12.5 - Collection of Pregnancy Information

12.5.1. Female subjects

- Investigator will collect pregnancy information on any female who becomes pregnant during the course of the study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 12.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication and be withdrawn from the study.

12.5.2. Female partners of male subjects

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.6. Appendix 12.6 - Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK3196165 or any concomitant medicines;
- Rheumatoid arthritis susceptibility, severity, and progression and related conditions.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been

identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained.
- Discontinue participation in the genetic research and destroy the genetic DNA sample.

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

References:

Chen H, Yu KD, Xu GZ. Association between variant Y402H in age-related macular degeneration (AMD) susceptibility gene CFH and treatment response of AMD: a meta-analysis. PLoS One 2012;7:e42464.

Gorin MB. Genetic insights into age-related macular degeneration: controversies addressing risk, causality, and therapeutics. Mol Aspects Med 2012;33:467-86.

12.7. Appendix 12.7 - Important Study Assessment Details & Study Specific Equipment

Joint Assessments
To prevent potential unblinding because of observed efficacy changes, a "dual assessor" approach will be used to evaluate efficacy and safety.

The Joint Assessor (or designee) should be a rheumatologist or other skilled arthritis assessor and will be responsible only for completing the joint counts. To ensure consistent joint evaluation throughout the trial, individual subjects should preferably be evaluated by the same joint assessor for all study visits.

The Treating Physician (or designee) should be a rheumatologist (or other medically qualified physician) and will have access to both safety and efficacy data. The Treating Physician will have access to source documents with the exception of the calculated DAS28(CRP) score, laboratory results with the exception of the CRP results from the central laboratory and eCRFs and will be responsible for completing Physician's Global Assessment of Disease Activity VAS, Morning stiffness assessment, and safety assessments (adverse events, vital signs, concomitant medications, review of laboratory data).

It is essential that assessments completed by the subject and Joint Assessor are made before those by the Treating Physician.

Quality of Life and Patient-Reported Outcomes
The questionnaires will be completed at relevant study visits as described in the Time and Events Table (Section 7.1), and the data will be directly entered into the ePRO.

The following services and hardware will be required:

Actigraphy
In this study, actigraphy data will be captured for a subset of subjects at participating sites by a commercially available, continuous logging, three-axis electronic accelerometer which will be provided to all sites. Actigraphy data will be collected throughout the study as described in the Time and Events Table (Section 7.1). The accelerometer will be placed on the subject upon visiting the clinic and will be worn by the subject continuously for up to 14 days of data collection. At the end of the data collection period, coinciding with a study visit, the accelerometer will be removed, the raw data downloaded, and the unit cleaned and recharged for reuse.

In addition, subjects that participate in the actigraphy assessments will be required to complete in parallel an RA Symptom and Impact Diary PRO. The provision and collection of these diaries will coincide with the placement of the accelerometer.

Spirometry/D_{LCO}
Equipment and site training for the standardised measurement of spirometry and D_{LCO} will be provided. Results will be sent from the site to the vendor for evaluation, who will then send the data to designee electronically.

Centralised ECG
Equipment and site training for the standardised measurement of ECGs will be provided. It is planned to collect and read the ECGs centrally.

12.8. Appendix 12.8 - Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 12.9 - Protocol Changes

Protocol Amendment: 01

Medical Monitor/Sponsor Information Page

Information concerning GSK Medical Monitor/SAE Contact Information removed.

Rationale

Details of Parexel Medical Monitor/SAE Contact Information were added to the Study Reference Manual.

Section 7.1. Time and Events Table

Scheduled assessments were revised.

Rationale

Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, HAQ-DI, and CRP, ESR were added at Weeks 28, 32, 40, 44, and 48, 12-lead ECG at EW; Spirometry (FEV1, FVC) at EW; D_{LCO} at Weeks 52, 62, and EW.

Appendix 12.7. PRO Questionnaires

Entire Appendix with examples of PRO Questionnaires removed.

Rationale

The Appendix only gave examples of the PRO Questionnaires, the actual versions used were programmed into electronic PRO (ePRO) devices.

Protocol Amendment: 02

Title page

Revision of the study title.

Rationale

Added "Double-Blind, Placebo-Controlled" to the study title, and removed "versus Placebo".

Section 3. Objective(s) and endpoint(s), Section 7.2. Screening and Critical Baseline Assessments, Section 7.3. Efficacy, Section 7.10.5. RA Symptom and Impact Diary PRO, 7.10.6. Exploratory Health Outcomes Assessment - Actigraphy, Appendix 12.7. Important Study Assessment Details & Study Specific Equipment.

Added “at participating sites”.

Rationale

Clarified that actigraphy will only be at participating sites.

Section 4.4. Type and Number of Subjects

Added “Study Reference Manual (SRM)”.

Rationale

Replaced “Study Procedures Manual SPM”, and throughout protocol.

Section 6.1. Investigational Product and Other Study Treatment.

Minor revisions to placebo and co-medications information.

Rationale

Replaced “Placebo (for blinding)” with “Control”; deleted “and will be provided by the study site” in reference to supply of saline; and deleted “MTX and folic acid will be sourced locally from commercial stock” as provision will vary by site.

Section 6.1.

Clarified guidance on dosing instructions.

Rationale

Revised text to “GSK3196165/placebo *should* be administered on the same day each week ± 1 day for the first 5 weekly doses *(with a minimum of 5 days between doses, for no more than 2 consecutive doses)*. Following this GSK3196165/placebo *should* be administered on the same day EOW ± 3 days *(with a minimum of 8 days between doses)*”; and “Subjects will be randomized as shown in Time and Events Table, Section 7.1, *and the dosing schedule should be followed as closely as possible*”.

Section 7.3.3. Patient’s Global Assessment of Arthritis

Revised anchor text.

Rationale

Replaced “no symptoms” with “very well” and “most severe disease activity” with “very poor” for consistency with other clinical studies.

Section 7.3.4. Physician’s Global Assessment of Arthritis

Revised anchor text.

Rationale

Replaced “no symptoms” with “none” and “most severe disease activity” with “extremely active” for consistency with other clinical studies.

Protocol Amendment: 03

Section 3. Objective(s) and endpoint(s), Section 7.1. Time and Events Table and Section 7.7. Biomarker(s)/Pharmacodynamic Markers

Removal of flow cytometry analysis.

Rationale

The logistics of incorporating flow cytometry into a large multi-centre, global study with all sites collecting and processing samples, the difficulties of ensuring standardisation of methodology, and hence concerns that the quality of data might be compromised led to the decision not to keep this assessment of biological activity of GSK3196165. Moreover, given the primary objective of this study is dose-finding, many subjects may be taking sub-therapeutic doses of GSK3196165.

Section 3. Objective(s) and endpoint(s)

The statements of “Pharmacodynamic biomarkers to assess biological response to GSK3196165 in serum” were revised to “Pharmacodynamic biomarkers which may be predictive of response to GSK3196165” and “Pharmacodynamic biomarkers to assess response to GSK3196165” with examples.

Rationale

The original statements were duplicate text, and revisions clarified the purpose and appropriate examples of biomarkers.

Section 4.7.1. Risk Assessment

Corrections to neutropenia levels.

Rationale

There were typographical errors in neutropenia (absolute neutrophil count) and lymphocytopenia thresholds, revised to align with values in Exclusion Criteria #25.

Section 5.1. Inclusion Criteria and Section 7.2. Screening and Critical Baseline Assessments

Clarification of TB testing.

Rationale

Clarification that TB tests may be performed locally.

Section 6.1. Investigational Product and Other Study Treatment and Section 6.8. Compliance with Study Treatment Administration

Removal of irrelevant information on administration of MTX at sites.

Rationale

Protocol already had statement that Investigators are responsible for ensuring that subjects continue to receive MTX and folic acid and Subjects will be given instructions on compliance and treatment with MTX. Added that the date taken and total weekly dose will be recorded in the eCRF.

Section 6.1. Investigational Product and Other Study Treatment, Section 6.5. Blinding, Section 6.7. Preparation/Handling/Storage/Accountability, Section 6.8. Compliance with Study Treatment Administration

Clarification of unblinded administrator.

Rationale

Examples given as study co-ordinator or nurse; pharmacist removed.

Section 6.5. Blinding

Clarification of shield.

Rationale

Examples given as eye mask or blindfold.

Section 6.8. Compliance with Study Treatment Administration

Addition of volume dosed to be recorded.

Rationale

Clarification that the date and time of each dose and volume administered in the clinic will be recorded in the eCRF.

Section 7.4.11. Clinical Safety Laboratory Assessments (Table 2 Routine Laboratory Assessments).

Corrected Routine Laboratory Assessments.

Rationale

Added Erythrocyte count, removed Albumin and Protein/creatinine ratio.

Protocol Amendment: 04

Section 7.1. Time and Events Table

Removal of blank line.

Rationale

Details of flow cytometry analysis had been deleted in Amendment 04, but the line in the Table had inadvertently been left.

Protocol Amendment: 05

Section 4.2. Treatment Arms and Duration and Section 5.4. Withdrawal/Stopping Criteria

Addition of mandated withdrawal at Week 38.

Rationale

Any subject not achieving EULAR good/moderate response at Week 36 will be withdrawn from the study at Week 38 to ensure that all continuing subjects are receiving effective treatment.

Section 4.5. Design Justification

Removal of abbreviation "SoC".

Rationale

Clarification that the abbreviation "SoC" is "standard of care".

Section 5.3.1. Re-Screening

Clarification of rescreening procedure.

Rationale

Clarification that entire rescreening is not required if chest X-ray within 12 weeks of the first screening period or HRCT within the first screening period.

Section 5.3.2.1. and Section 5.3.2.1. Laboratory tests and D_{LCO} test

Split Section 5.3.2. into two parts.

Rationale

Clarification that if the D_{LCO} repeat test cannot be done within the screening window, then the subject must be re-screened.

Section 7.1. Time and Events Table and Section 7.4.11. Clinical Safety Laboratory Assessments (Table 2 Routine Laboratory Assessments)

Added lipid measurements.

Rationale

Recent European guideline (CPMP/EWP/556/95 Rev. 2, June 2015) on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis proposes "The influence of the new drug on lipids and atherogenic potential need to be monitored." Cholesterol, Triglycerides, High-density lipoprotein (HDL) and Low-density lipoprotein (LDL) added at Baseline, W12, W24, W52, W62, and EW.

Section 7.1. Time and Events Table

Clarification of header version numbers and footnotes.

Rationale

Previous version of protocol had an incorrect header version. W62 visit corrected to D435 rather than D470. Footnotes revised to clarify that Chest X-ray or Chest HRCT not required to be repeated if subject re-screened; and >8h fasting required before blood draw for lipid assessments.

Section 7.3.5. DAS Assessments

Clarification of eligibility.

Rationale

Confirmation that the screening and Day 1 DAS28(ESR) scores will be confirmed by the IRTS for eligibility of subjects for randomization.

Section 7.4.7. Pregnancy

Clarification of any pregnancy.

Rationale

Clarification that any pregnancy includes participating females and female partners of participating males.

Appendix 12.1. Abbreviations and Trademarks

Added abbreviations.

Rationale

Abbreviations for disease-related event, high-density lipoprotein, and low-density lipoprotein missing from list.

Appendix 12.2. Contraception eligibility criteria for female and male subjects

Clarification of methods of contraception and required documentation.

Rationale

Alignment with new GSK template.

Appendix 12.5. Collection of Pregnancy Information

Clarification that any female subject who becomes pregnant while participating will discontinue study medication and be withdrawn from the study.

Rationale

Previous statement did not include discontinuation of study medication.

Appendix 12.9. Protocol Changes

Appendix added to track all protocol text changes.

Rationale

Expanded explanation of all changes rather than just a summary at the beginning of the protocol.

Protocol Amendment: 06

Section 5.1. Inclusion Criteria

Clarification that the D_{LCO} tests may be repeated twice within the screening period.

Rationale

To avoid any misunderstanding that there are three permitted tests in total.

Section 5.2. Exclusion Criteria and Section 5.4.2. QTc Stopping Criteria

Clarification that that only Fridericia's formula (QTcF) will be used.

Rationale

Recent FDA/ICH Guidance for Industry (October 2012) "E14 Clinical Evaluation of QT/QTc" states "In adults, Bazett's correction has been clearly shown to be an inferior method of correcting for differences in heart rate among and within subjects. Therefore, QT interval data corrected using Bazett's corrections is no longer warranted in all applications unless there is a compelling reason for a comparison to historical Bazett's corrected QT data. Presentation of data with a Fridericia correction is likely to be appropriate in most situations, but other methods could be more appropriate."

Section 5.3.2.3. ECG Test

Clarification that the ECG test may be repeated once within the screening period.

Rationale

To permit a repeat screening ECG if the QTcF value is slightly out of range, provided no other clinically-significant abnormalities are noted.

Section 7.1. Time and Events Table

Clarification of footnotes.

Rationale

Clarification that ECG should be performed before vital signs, blood draws, and dosing; that some Day 1 assessments may be performed up to 24 hours before dosing GSK3196165; and that blood sampling on Day 3 can be drawn ±1 day.

Section 7.7. Biomarker(s)/Pharmacodynamic Markers

Deletion of IL-22.

Rationale

Considered not essential as we are also measuring IL-23.

Appendix 12.2. Contraception eligibility criteria for female and male subjects

Clarification of required secondary method of contraception if using oral contraceptives.

Rationale

A sentence had been inadvertently deleted in the previous amendment's revisions.

Protocol Amendment: 07

Section 4.2 Treatment Arms and Duration and Section 6.4. Subject Specific Dose Adjustment Criteria

Removed the example formula to calculate the EULAR good/moderate response at Week 12 and Week 36, and inserted a table (and reference) to show requirements for EULAR good/moderate responses.

Rationale

The example formula was incorrect.

Section 5.1. Inclusion Criteria, Section 5.3.2.2. D_{LCO} test, Section 7.1. Time and Events Table, and Section 7.4.1. Screening visit(s)

Clarification that chest HRCT must be performed if D_{LCO} ≥60% to <70% predicted.

Rationale

To avoid any misunderstanding of requirement for chest HRCT.

Section 11. References

Updated IB document number, and added reference for EULAR good/moderate response**.**

Rationale

New version of IB, and revised formula for EULAR good/moderate response.