TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase IIa, Double-Blind, Mechanistic Study of GSK3196165 in Combination with Methotrexate Therapy in Subjects with Active Rheumatoid Arthritis Despite Treatment with DMARDs

Compound Number: GSK3196165

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Revision Chronology

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2015N261421_00	2015-DEC-16	Original
2015N261421_01	2016-MAR-01	Amendment No. 1
This amendment includes classification of primary and secondary objectives and endpoints in Section 1 and Section 3; extension of the screening window to six weeks in Section 1, Section 4.1, Section 5.3.1, Section 7.1, and Section 7.2; correction of several typographical errors; clarification of likely numbers of patients screened in Section 4.3; correction of >15% relative decrease in D_{LCO} as a trigger point in Section 4.6.1; clarification of D_{LCO} testing in Section 5.1, Section 5.3.2.2, Section 7.1, Section 7.2, and Section 7.6.12; addition of Day 1 joint count and correction of mandatory chest HRCT if D_{LCO} ≥60% - <70% predicted in Section 5.1; revision that subjects must have passed all screening assessments (including laboratory tests) prior to undertaking MRI scanning, and that whole blood flow cytometry is scheduled on Day 1 in Section 7.1; an additional Exclusion Criterion for MRI in Section 5.2; correction that re-screening is permitted in Section 5.3.1; correction that RNA analysis is not part of the pharmacogenetics substudy in Section 7.1 and Section 7.2; clarification of the RA Symptom and Impact Diary in Section 7.5.2; clarification of PK sample in Section 7.2; clarification of MRI image processing in Section 7.9; clarification of abbreviations in Appendix 12.1; revision of contraception guidance in Appendix 12.2; and clarification of data recording in Appendix 12.7.		

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March 1st 2016

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205180

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 205180

Rationale

This study is designed to explore the activity of granulocyte-macrophage colony stimulating factor (GM-CSF) signaling pathway in subjects with rheumatoid arthritis (RA), and the potential impact of inhibition of this axis by GSK3196165. An additional exploratory aim is to evaluate whether there are any differences in the GM-CSF axis between subjects with early RA compared with those with more established disease.

Finally, this study aims to establish the potential impact of GSK3196165 on inflammatory structural joint damage in the hand/wrist using magnetic resonance (MR) imaging (MRI).

Objective/Endpoints

Primary objectives	**Primary endpoints**
The main objectives of this study are to explore the activity of GM-CSF signaling pathway characterized by exploratory biomarkers in subjects with RA, the impact of GSK3196165 therapy, and whether there are any differences in this GM-CSF signaling pathway between subjects with early RA or established RA.	• Changes from baseline in exploratory biomarkers.
Secondary objectives	**Secondary endpoints**
To evaluate the safety and tolerability of GSK3196165 in subjects with RA.	• Incidence of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs). • Immunogenicity (anti drug antibodies [ADAs]).
To evaluate the impact of GSK3196165 on inflammatory structural joint damage in the hand/wrist using MRI.	• Change from baseline in synovitis, osteitis and erosion as assessed by Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring system (RAMRIS) and rheumatoid arthritis MRI quantitative score (RAMRIQ) in the most affected hand/wrist.
Exploratory Biomarker Endpoints*	
• Identify/validate markers of downstream signaling of GM-CSF and/or potential novel markers for GSK3196165 activity. • Pharmacodynamic biomarkers to assess response to GSK3196165 (*e.g.* may include, but not limited to, interleukin [IL]-1β, tumor necrosis factor alpha [TNFα], IL-6, IL-8, IL-15, IL-23, IL-17A/F; chemokines such as CCL17, CXCL4, CXCL7, CXCL13, CCL22; and complement proteins such as C5a, ratio C3/C3dg, TCC, C4, C4a, sCD163). • Effect of GSK3196165 on target cell populations (*e.g.* may include, but not limited to,	

circulating levels of T, B, natural killer (NK), Th17, T regulatory cells and activated monocytes, dendritic cells, neutrophils).
- Whole blood ribonucleic acid (RNA) markers of engagement (*e.g.*, serum concentration of free GM-CSF/macrophage signaling and response to GSK3196165.
- Whole blood deoxyribonucleic acid (DNA) analysis to explore the relationship between genetic variants in the host and response to GSK3196165.
- Biomarkers of extracellular matrix (ECM) or aggrecan degradation (*e.g.* may include, but not limited to, serum chondrex [YKL-40] also called human cartilage glycoprotein 39 [HC gp 39], ARGS neoepitope).
- Biomarkers which may be indicative of RA disease activity (*e.g.*, may include, but not limited to 14-3-3η, anti-cyclic citrullinated protein antibody [ACPA], C-reactive protein [CRP], rheumatoid factor [RF]).
- Pharmacodynamic biomarkers which may be predictive of response to GSK3196165 (*e.g.* may include, but not limited to, C1M, C2M, C3M, CRPM, VICM, MRP8/14, matrix metalloproteinase 3 [MMP-3], 14-3-3η).

Exploratory MRI/Imaging Endpoints*

- Change from baseline in joint inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:
  - Exchange rate (K^{trans})
  - Interstitial volume (V_e)
  - Plasma volume (V_p)
  - Initial rate of enhancement (IRE)
  - Maximal signal intensity enhancement (ME).

Exploratory Clinical Efficacy Endpoints*

- Change from baseline at all assessment timepoints for:
  - ACR20/50/70** response rates
  - Disease activity score for 28 different joints with CRP value (DAS28[CRP]) score
  - DAS28(CRP) remission rates and categorical (European League Against Rheumatism [EULAR] good/moderate) response.

Note: For composite endpoints, *e.g.*, DAS28(CRP), American College of Rheumatology (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).

Pharmacokinetic/Target Engagement Endpoints

- GSK3196165 pharmacokinetic (PK) parameters derived from the sparse blood samples and using a population PK analysis.
- Pharmacodynamic biomarkers to assess target engagement (TE) (*e.g.*, serum concentration of free GM-CSF, GM-CSF: GSK3196165 complex).

Exploratory Safety Endpoints

• To evaluate potential biomarkers of pulmonary alveolar proteinosis (PAP) pathogenesis.	• Biomarkers which may be predictive of lung damage (*e.g.*, Krebs von den Lungen-6 [KL-6], serum amyloid A (SAA), surfactant protein-D [SP-D], cholestenoic acid). • GM-CSF auto-antibodies.

*Where relevant, comparisons will be made between the early and established RA subject populations.
**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.

Overall Design

This is a randomized Phase IIa, multi-center, double-blind, placebo-controlled parallel group study to explore the mechanistic evidence that the GM-CSF signaling pathway is active in subjects with RA, and the potential impact of inhibition of this axis by GSK3196165. In addition, the study will assess the potential impact of GSK3196165 on inflammatory structural joint damage in the most affected hand/wrist using MRI.

The randomization will be stratified by early or established disease (see below) and randomization will occur at the baseline visit on Day 1.

Treatment Arms and Duration

- Screening period up to 6 weeks, then 10-week combination dosing with methotrexate (MTX), with a 12-week follow-up visit after the last dose (Week 22).
- GSK3196165 180 mg *vs.* placebo administered by subcutaneous (SC) injection, given weekly for 5 weeks, then every other week thereafter until Week 10.

Type and Number of Subjects

- Approximately 40 subjects with active RA despite treatment with DMARDs (including conventional or biologic) will be randomized into the study.
- Ideally, 50% of subjects enrolled into the study should have early RA (≤2 years since diagnosis). The actual proportion will be monitored throughout the study and randomization may be altered if the projected final proportion with early RA is less than 30%.
- Subjects will be randomized on a 3:1 basis to GSK3196165 or placebo.
- Randomization will be stratified by early RA (≤2 years since diagnosis) and established RA.

Analysis

All endpoints are exploratory. They will be summarized for the overall population as well as by RA status (early *vs.* established). GSK3196165 treatment effect will be measured by change from baseline. They will be presented by tables and figures. The relationships between endpoints will be graphically explored (and further quantified if permitted by adequate data). Bayesian methods will be used to explore the probabilistic aspect of certain endpoints.

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. Study Rationale

This study is designed to explore the activity of the GM-CSF signaling pathway in subjects with RA, and the potential impact of inhibition of this axis by GSK3196165. An additional exploratory aim is to evaluate whether there are any differences in the GM-CSF axis between subjects with early RA (≤2 years since diagnosis) compared with those with more established disease.

Finally, this study aims to establish the potential impact of GSK3196165 on inflammatory structural joint damage in the hand/wrist using magnetic resonance imaging (MRI).

2.1.1. Rheumatoid Arthritis

RA is a chronic, systemic inflammatory autoimmune disease, characterized by asymmetrical 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 MTX is the gold standard, and biological DMARDs which target cytokines (*e.g.* tumor necrosis factor alpha [TNFα], interleukin [IL]-6), B-cells or T-cells. However, a substantial proportion of subjects 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 subject'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 cell surface major histocompatibility complex (MHC) class II heterodimers 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 cell surface MHC class II heterodimers on antigen presenting cells, which in turn will activate $CD4^+$ T cells. In addition, GM-CSF is a strong chemoattractant factor for neutrophils and induces the release of reactivated 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]. Moreover, there is evidence that early RA is the result of an already-established synovitis in which macrophage-derived cytokines play an important role in the clinical signs of inflammation [Tak, 1997].

In mouse models of collagen-induced arthritis (CIA), anti-GM-CSF treatment reduced disease activity and prevented progression of established arthritis [Cook, 2001; Plater-Zyberk, 2007] and, furthermore, administration of recombinant GM-CSF led to exacerbation of arthritis [Campbell, 1997]. Importantly, anti-GM-CSF was shown to be beneficial for either early or established arthritis [Cook, 2001]. Moreover, GM-CSF depletion appeared to have a more dramatic effect than depletion of TNF since only 2/15 (13%) of GM-CSF-deficient mice developed CIA compared with 8/26 (31%) of TNF-deficient mice [Campbell, 1998; Campbell, 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 (particularly in the early stages of RA), 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 neutralizes 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 four completed clinical trials to date, summarized in the IB (GSK Document Number 2014N190256_01), and one ongoing clinical trial (201755).

MSC-1001 was a Phase1b/2a multi-center, randomized, sequential group, double-blind, placebo-controlled study which evaluated the safety, preliminary efficacy, and pharmacokinetic (PK) of multiple doses of GSK3195165 in subjects (N=96) with active, mild-moderate RA [Behrens, 2015]. 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 C-reactive protein (CRP) >5 mg/L (in sero-negative subjects) or CRP >2 mg/L (in rheumatoid factor (RF) and/or anti-cyclic citrullinated protein antibody (ACPA) sero-positive subjects) and disease activity score for 28 different joints (DAS28) score ≤5.1. Subjects received four weekly intravenous (IV) 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 at 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 (TEAEs) 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 adverse events (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 pulmonary function tests (PFTs) or diffusing capacity of the lung for carbon monoxide (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 subjects recovered.

An ongoing phase IIb, double-blind, placebo-controlled, dose-adaptive, study of the efficacy and safety of GSK3196165 in combination with MTX therapy, in subjects with active moderate to severe RA despite treatment with MTX. Study 201755 commenced in July 2015 with doses of GSK3196165 from 22.5 mg up to 180 mg. A total of 210 methotrexate-inadequate response (MTX-IR) patients with moderate-severe RA are planned to be enrolled.

3. OBJECTIVE AND ENDPOINTS

Primary objectives	**Primary endpoints**
The main objectives of this study are to explore the activity of GM-CSF signaling pathway characterized by exploratory biomarkers in subjects with RA, the impact of GSK3196165 therapy, and whether there are any differences in this GM-CSF signaling pathway between subjects with early RA or established RA.	• Changes from baseline in exploratory biomarkers.
Secondary objectives	**Secondary endpoints**
To evaluate the safety and tolerability of GSK3196165 in subjects with RA.	• Incidence of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs). • Immunogenicity (anti drug antibodies [ADAs]).
To evaluate the impact of GSK3196165 on inflammatory structural joint damage in the hand/wrist using MRI.	• Change from baseline in synovitis, osteitis and erosion as assessed by Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring system (RAMRIS) and rheumatoid arthritis MRI quantitative score (RAMRIQ) in the most affected hand/wrist.
Exploratory Biomarker Endpoints*	
• Identify/validate markers of downstream signaling of GM-CSF and/or potential novel markers for GSK3196165 activity. • Pharmacodynamic biomarkers to assess response to GSK3196165 (*e.g.* may include, but not limited to, IL-1β, TNFα, IL-6, IL-8, IL-15, IL-23, IL-17A/F; chemokines such as CCL17, CXCL4, CXCL7, CXCL13, CCL22; and complement proteins such as C5a, ratio C3/C3dg, TCC, C4, C4a, sCD163). • Effect of GSK3196165 on target cell populations (*e.g.* may include, but not limited to, circulating levels of T, B, natural killer (NK), Th17, T regulatory cells and activated monocytes, dendritic cells, neutrophils). • Whole blood ribonucleic acid (RNA) markers of engagement (*e.g.*, serum concentration of free GM-CSF/macrophage signaling and response to GSK3196165. • Whole blood deoxyribonucleic acid (DNA) analysis to explore the relationship between genetic variants in the host and response to GSK3196165. • Biomarkers of extracellular matrix (ECM) or aggrecan degradation (*e.g.* may include, but not limited to, serum chondrex [YKL-40] also called human cartilage glycoprotein 39 [HC gp 39], ARGS neoepitope). • Biomarkers which may be indicative of RA disease activity (*e.g.*, may include, but not limited to 14-3-3η, ACPA, CRP, RF). • Pharmacodynamic biomarkers which may be predictive of response to GSK3196165 (*e.g.* may include, but not limited to, C1M, C2M, C3M, CRPM, VICM, MRP8/14, matrix metalloproteinase 3 [MMP-3], 14-3-3η).	

Exploratory MRI/Imaging Endpoints*	

• Change from baseline in joint inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:
  • Exchange rate (K^{trans})
  • Interstitial volume (V_e)
  • Plasma volume (V_p)
  • Initial rate of enhancement (IRE)
  • Maximal signal intensity enhancement (ME).	

Exploratory Clinical Efficacy Endpoints*	

• Change from baseline at all assessment timepoints for:
  • ACR20/50/70** response rates
  • Disease activity score for 28 different joints with CRP value (DAS28[CRP]) score
  • DAS28(CRP) remission rates and categorical (European League Against Rheumatism [EULAR] good/moderate) response.
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).	

Pharmacokinetic/Target Engagement Endpoints	
• GSK3196165 PK parameters derived from the sparse blood samples and using a population PK analysis. • Pharmacodynamic biomarkers to assess target engagement (TE) (*e.g.*, serum concentration of free GM-CSF, GM-CSF: GSK3196165 complex).	
Exploratory Safety Endpoints	
• To evaluate potential biomarkers of pulmonary alveolar proteinosis (PAP) pathogenesis.	• Biomarkers which may be predictive of lung damage (*e.g.*, Krebs von den Lungen-6 [KL-6], serum amyloid A (SAA), surfactant protein-D [SP-D], cholestenoic acid). • GM-CSF auto-antibodies.

*Where relevant, comparisons will be made between the early and established RA subject populations.
** 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.

4. STUDY DESIGN

4.1. Overall Design

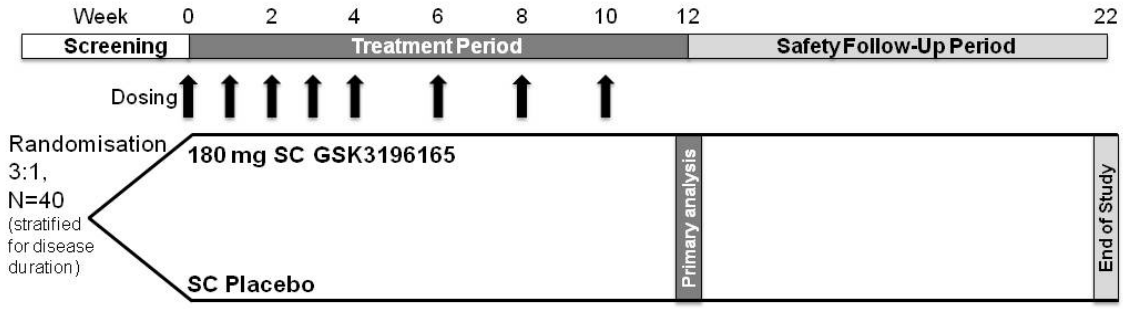
This is a randomized Phase IIa, multi-center, double-blind, placebo-controlled parallel group study to explore the mechanistic evidence that the GM-CSF signaling pathway is active in subjects with RA, and the potential impact of inhibition of this axis by GSK3196165. In addition, the study will assess the potential impact of GSK3196165 on inflammatory structural joint damage in the most affected hand/wrist using MRI.

Approximately 40 subjects with active RA despite treatment with DMARDs (including conventional or biologic) will be randomized into the study, following a screening period

of up to 6 weeks. The total treatment period is up to 10 weeks, with a 12-week follow-up period after the last dose (Week 22). Ideally, 50% of subjects enrolled into the study should have early RA (*e.g.* ≤2 years since diagnosis). The actual proportion will be monitored throughout the study and randomization may be altered if the projected final proportion with early RA is less than 30%.

A schematic representation of the study design is shown in Figure 1.

Figure 1 Study design



4.2. Treatment Arms and Duration

Subjects will be randomized on a 3:1 basis to GSK3196165 or placebo. Subjects will receive GSK3196165 180 mg or placebo once weekly for 5 weeks, and then every other week until Week 10.

In addition to GSK3196165 or placebo, subjects will receive MTX 7.5–25 mg/week and folic (or folinic) acid ≥5 mg/week during the combination treatment period.

Details of the study treatment are presented in Section 6.

4.3. Type and Number of Subjects

Approximately 80 subjects with active early/established RA despite treatment with DMARDs will be screened (subjects can be rescreened once) to achieve 40 randomized subjects. Rescreening criteria are listed in the Study Reference Manual (SRM).

4.4. Design Justification

This mechanistic study is designed to better understand the efficacy of GSK3196165 as a treatment option for RA (and in particular for subjects with early disease).

The main objectives of this study are to explore the activity of GM-CSF signaling pathway characterized by exploratory biomarkers) in subjects with RA, the impact of GSK3196165 therapy, and whether there are any differences in this GM-CSF signaling pathway between subjects with early RA or established RA.

Exploratory endpoints include:

- Identification of biomarkers of downstream signaling of GM-CSF;
- Pharmacodynamic biomarkers to assess response to GSK3196165;
- Effect of GSK3196165 on target cell populations;
- Analysis of whole blood ribonucleic acid (RNA) markers of engagement (*e.g.* serum concentration of free G-CSF /macrophage signaling and response to GSK3196165;
- Analysis of whole blood DNA to explore the relationship between genetic variants in the host and response to GSK3196165;
- Biomarkers which may be indicative of RA disease;
- Pharmacodynamic biomarkers which may be predictive of response to GSK3196165.

Additionally, exploratory MRI imaging (including DCE-MRI, the OMERACT RAMRIS [Østergaard, 2003], and the RAMRIQ system [Bowes, 2014]) will be employed to explore a potential effect of GSK3196165 on disease modification (which includes a reduction in inflammation in terms of synovitis and bone marrow lesions, structural progression in terms of cartilage space loss (as an analog of joint space narrowing).

All study endpoints will be evaluated throughout the study and at Week 12, following the completion of dosing at Week 10, to assess the efficacy of GSK3196165. A follow-up (observational) period will then take place, completing the study at Week 22.

Justification of placebo control is detailed in Section 4.5.2.

4.5. Dose Justification

4.5.1. GSK3196165

- The dosing regimen for this study includes five subcutaneous (SC) loading doses of GSK3196165 180 mg administered every week, followed by three doses of 180 mg SC administered every other week. The predicted PK plasma profile of GSK3196165 using this dosing regimen is shown in Figure 2 below. This regimen was selected to i) produce sufficient drug exposure in both plasma and synovial fluid to inhibit free GM-CSF from binding to its receptor, and ii) be associated with an appropriate margin to the no observed adverse effect level (NOAEL) and the no observed effect level (NOEL) (the dose at which foamy alveolar macrophages were not observed in the 13-week cynomolgus monkey study; see IB (GSK Document Number 2014N190256_01).
- The predicted exposures associated with the proposed dosing regimen over 10 weeks, allows a 30-fold margin to the NOAEL and a 10-fold margin to the NOEL in preclinical studies of similar duration. In addition, a dose of 180 mg SC is predicted to result in steady-state exposures which will allow an approximate 26-fold margin to the NOAEL, and a three-fold margin to the NOEL based on the

findings in the 26-week monkey study. Of note, in the monkey 26-week study, full reversibility of the foamy alveolar macrophages was observed following clearance of GSK3196165. The IV 4-week monkey study provides additional safety cover for the weekly loading dosing phase of the proposed clinical study (Table 1).

Figure 2 Predicted GSK3196165 Plasma Concentrations at the Recommended Dosing Regimen (Median and 95% Confidence Interval)

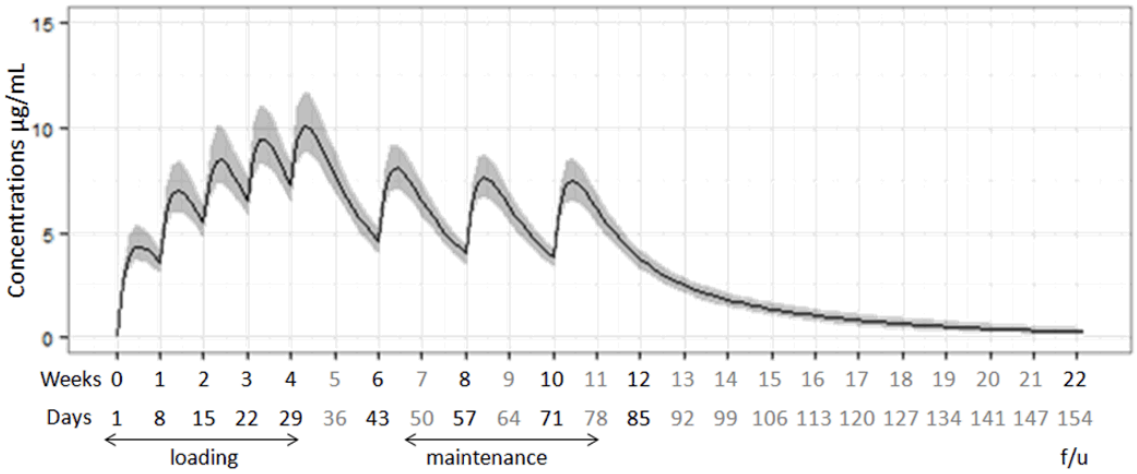


Table 1 Safety Margins with 180 mg SC GSK3196165 Relative to Exposures in Non-clinical Toxicology Studies

Study	Species	Assessment	Dose (mg/kg/wk)	$AUC_{(0\text{-}336)}$ 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	Not applicable
			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 MOR103C10 4 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		

$AUC_{(0-336)}$=Area under drug concentration time curve from time zero to 336 hours postdose; IV intravenous; QW=once a week; SC subcutaneous

a. Simulated mean area under the plasma concentration time curve (AUC) based on analysis of SC and IV data for doses ≥0.5 mg/kg from study MSC-1000 (N=18) and study MOR103C104 (N=32) with a two compartment model and calculation of F by ratio of intravenous plasma clearance/subcutaneous plasma clearance (Cl_{IV}/Cl_{SC}) 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 area under drug concentration time curve from time zero to 168 hours postdose ($AUC_{[0-168]}$) values have been used and multiplied by two to obtain mean concentrations over a two-week period
c. No observed adverse effect dose level (NOAEL)
d. No observed effect dose level (NOEL)

4.5.2. Placebo

Placebo control (on methotrexate background) is required for this study in order to provide an adequate internal control and reference group for the analysis of changes in biomarkers. This is of particular importance given the exploratory nature of the biomarker tests being used in this study.

Both the 3:1 randomization ratio and the treatment duration of 10 weeks will minimize the exposure to placebo in the study. If a subject experiences an unacceptable level of disease activity during the study, the investigator may withdraw the subject at any point.

4.5.3. Methotrexate Background

All subjects will continue to receive MTX (and folic or folinic acid) throughout the study.

4.6. 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.

4.6.1. 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-tumor necrosis factor [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 TB 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 investigational product	**Subject selection:** • Subjects with active infections or a history of recent or recurrent infections are not permitted to enter the study. • Subjects with significant leukopenia (white blood cell count ≤3.0 x10^9/L) and neutropenia (absolute neutrophil count ≤1.5 x 10^9/L) are not permitted to enter the study. • Subjects will be screened for *Mycobacterium tuberculosis* (TB), human immunodeficiency virus (HIV) and Hepatitis B and C, and excluded from study participation if positive. Subjects with any past history of TB or Hepatitis B will also be excluded. • Investigators are expected to assess vaccination status, including against influenza and pneumococcus, according to local guidelines. **Subject monitoring:** • Serious infections are categorized as AESIs. • Subjects will be closely monitored for infections and additional information to clarify the events will be recorded in the electronic case report form (eCRF). Appropriate diagnostic tests will be considered during the study if clinically indicated to ensure

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	(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.	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 subject Informed Consent Form. **Withdrawal criteria:** • In the event of a serious infection, study medication should be discontinued and the subject withdrawn from the study.
Pulmonary alveolar proteinosis	GM-CSF signaling is required to maintain the normal function of alveolar macrophages. Long-term absence of GM-CSF signaling (*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. However, GSK believes that anti-GM-CSF therapy has a low risk of PAP development, for the following reasons: • Auto-antibodies to GM-CSF (GMAbs) have been shown to occur in healthy people at low levels, and the critical threshold of GMAbs associated with the presence of PAP is ~10µg/mL [Uchida, 2009], and a serum threshold of >5µg/mL has been reported as the optimal cut	**Subject selection** • 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 during screening in order to exclude those subjects with impairment. Subjects with abnormal D_{LCO} or forced expiratory volume in one second (FEV1) will be excluded. **Dose Duration:** • The exposure duration to GSK3196165 in this study is 10 weeks. Although the time course of PAP development in humans is unknown, the published literature suggests that it requires full inhibition of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	off value for distinguishing autoimmune PAP serum from normal serum [Uchida, 2014]. • A recent study has reported that individual auto-antibodies from patients only partially-neutralized GM-CSF and when injected into mice together with human GM-CSF led to the accumulation of a large pool of circulating GM-CSF that remained partially bioavailable [Piccoli, 2015]. In contrast, a combination of three non-cross-competing antibodies completely neutralized GM-CSF activity in vitro by sequestering the cytokine in high-molecular-weight complexes, and in vivo promoted the rapid degradation of GM-CSF-containing immune complexes in an Fc-dependent manner. These findings provide a plausible explanation for the severe phenotype of PAP patients and for the low likelihood of treatments based on single anti-GM-CSF monoclonal antibodies causing PAP. **Non-clinical Data:** Non-adverse minimal to mild foamy alveolar macrophage accumulation was noted in lungs of monkeys in the 13-week SC and 26-week intravenous (IV) toxicology studies, but reversed following off drug period. Dose levels at which foamy alveolar macrophages were not	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 during screening, at 12 weeks, and at the follow-up visit. Relative decrease in D_{LCO} >15% from screening will be reported as an AESI if confirmed with three consecutive weekly tests. • In the event of any new or clinically significant pulmonary abnormalities that may develop during the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	study and persist for three consecutive weeks (*e.g.*, increased shortness of breath/dyspnea, or unexplained and persistent coughing), the subject will be withdrawn from study drug for the remainder of the study and it is recommended that the subject be referred to a pulmonologist for further assessment. The subject should be followed until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined. 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:** • 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**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 three 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 subject Informed Consent Form. • Should hypersensitivity or anaphylaxis occur, subjects should be managed appropriately per local guidelines/medical judgment. • Severe or serious hypersensitivity or anaphylaxis is categorized as AESIs. **Subject Monitoring:** • Subjects should be monitored for hypersensitivity reactions throughout the study, and the information recorded in the eCRF. • Any clinically significant event should be reported as an AE. **Withdrawal Criteria:** • In the event of severe or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		serious hypersensitivity 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 and 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.
Immunogenicity	**Pre-clinical Data:** ADAs to GSK3196165 were detected in some monkeys and was associated with reduced serum levels of GSK3196165; ADA associated toxicity was not observed. **Clinical Data:** In Study MSC1000, one healthy volunteer who received a single dose of 25 µg/kg was found to have an immunoglobulin M (IgM) ADA at Day 15, and in Study MSC1001 immunoglobulin G (IgG) ADA were detected at Week 13, but not Week 16 in one RA subject who received 4 weekly doses of 1.0 mg/kg, with no impact on GSK3196165 serum concentrations.	**Investigate Risk:** • Samples (pre- and post-baseline) will be collected from all subjects during the study to assess development of anti-drug antibodies and will be analyzed at the end of the study. • In addition to scheduled immunogenicity assessments, "event-driven" testing will also be employed for those subjects that experience anaphylaxis, serious hypersensitivity or adverse events that deemed to be clinically significant in the opinion of the investigator, and related to study drug administration that lead to withdrawal from the study, blood samples will be taken for immunogenicity testing at the time of the event and again 10 weeks after.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 and Clinical Data:** There have been no reports of neutropenia or decreases in leukocytes in the non-clinical and clinical GSK3196165 program.	**Subject Selection:** • Subjects with significant leukopenia (white blood count (WBC) ≤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 (see Time and Events Table, Section 7.1). • Grade 3 or 4 neutropenia is categorized 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, embryofetal or effects on fertility were noted in the reproductive toxicology studies using the surrogate rat anti-mouse GM-CSF monoclonal antibody, 22E9.	**Subject Selection:** • Male and female subjects will only be permitted to enter the study if they meet the contraception requirements detailed in inclusion criterion #8. • In addition, females of child bearing potential will undergo pregnancy testing at screening and at regular intervals during the study (see Time and Events Table, Section 7.1). • Due to concomitant use of methotrexate, additional precautions to avoid pregnancy in females of reproductive potential and female partners of males subjects enrolled in the study are required (see

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The effect on human pregnancy is unknown. **Clinical Data:** No healthy volunteers or RA subjects became pregnant during the studies, but one multiple sclerosis subject 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.	Appendix 12.2). **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 elective termination of a pregnancy will be reported as an AE or SAE.
Potential drug interaction with CYP450 substrates	**Non-clinical Data:** Cytokines can produce concentration-dependent inhibition on various CYP isoforms at the transcription level or by alteration of CYP enzyme stability in patients with infection or inflammation, and increase the plasma concentrations of specific CYP substrate drugs. Cytokine modulators may reverse the apparent "inhibition" effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP activities. GSK3196165 is a cytokine modulator, so has the potential to 'normalise' CYP expression from a suppressed state in patients with a pro-inflammatory disease (RA). **Clinical Data:**	**Subject Selection:** • Subjects of reproductive potential using hormonal contraceptives, including oral, injections, implants, and patches are required to use a secondary method of contraception. • Subjects receiving concomitant CYP450 substrate with narrow therapeutic index should be monitored for signs in changes in drug exposure (see Section 6.10).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No studies have been performed specifically to evaluate the potential for GSK3196165 to indirectly elicit a pharmacokinetic drug interaction through cytokine regulation of cytochrome P450 (CYPs) or drug transporter expression.	
Malignancy	The risk of malignancy is increased in subjects with RA. In addition, immunomodulatory therapies may increase the risk of malignancy. **Non-clinical and Clinical Data:** There have been no reports of malignancy in the non-clinical and clinical GSK3196165 program.	**Subject Selection:** • 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.
Gadolinium (Gd)-containing MRI contrast agents	**Non-clinical Data:** Animal studies have shown reproductive toxicity of Gd-containing MRI contrast agents at repeated high doses. **Clinical Data:** Use of MRI contrast agents in subjects with severely impaired renal function (GFR <30mL/minute) has been associated with Nephrogenic Systemic Fibrosis (NSF). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed against the risks. Gd contrast agents can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations, and	**Subject Selection:** • Pregnant or breast feeding females will be excluded from taking part in the study. • Subjects with impaired renal function (glomerular filtration rate (GFR) <60mL/minute) are excluded by the eligibility criteria. • Subjects with history of sensitivity to Gd-containing contrast agents will be excluded from the study. The MRI procedure will be conducted under the supervision of a trained and qualified clinical staff trained to appropriately manage an allergic reaction. • Sites will be responsible for following any additional

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	ranging to severe reactions including shock. In general, subjects with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions. The risk of hypersensitivity reactions may be higher in case of: • previous reaction to contrast media • history of bronchial asthma • history of allergic disorders Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely observed.	safety information for the specific gadolinium contrast agent used at their site and not enroll subjects if contraindicated. **Subject Monitoring and Management:** • MRI contrast at a dose less than or equal to 0.1 mmol/kg will be used in the MRI protocol. • Effective contraception is required during the study, and pregnancy tests will be performed regularly throughout the study prior to dosing in females of child bearing potential.
Exposure to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner.	**Subject Selection:** • All participants will be screened according to local hospital criteria and trial inclusion/exclusion before entering the MRI room to ensure they are able to have the MRI conducted. Subjects with non-magnetic resonance compatible metal implants or implantable electronic devices (*e.g.* pacemaker, defibrillator) will not be included in this study.

4.6.2. 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, most of whom had received prior DMARDs or biologics [Behrens, 2015]. In addition, mavrilimumab (an anti-GM-CSF α-subunit receptor mAb), in combination with MTX, has also shown substantial activity in RA subjects who had an inadequate response to MTX in studies of up to 2.4 years of dosing [Burmester, 2013; Burmester, 2014; Burmester, 2015] and namilumab (an anti-GM-CSF mAb) for 4 weeks [Huizinga, 2015]. These data support the clinical evaluation of GSK3196165 in subjects with RA.

4.6.3. 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-GM-CSF 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 up to 2.4 years in combination with MTX in subjects with active RA [Burmester, 2013; Burmester, 2014; Burmester, 2015] and namilumab [Huizinga, 2015] 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 subjects with autoimmune diseases, such as RA.

In addition, in accordance with routine pharmacovigilance, and internal GSK safety review team (SRT) will review blinded safety data, including clinical laboratory parameters and AEs, approximately monthly during the period of study conduct.

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.

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:

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Meets ACR/EULAR 2010 RA Classification Criteria **AND** Subject not diagnosed before age of 16 years.
3. Functional class I, II or III defined by the 1992 ACR Classification of Functional Status in RA.
4. Active disease as defined by: a. Swollen joint count of ≥4 (66-joint count) and tender joint count of ≥4 (68-joint count) at screening and at Day 1. **AND** b. DAS28(CRP) ≥3.2 at screening. **AND** c. CRP ≥3.0 mg/L.
5. Signs of inflammation such as synovitis in the MRI scan of the most-affected hand.
6. Must be currently taking MTX (15-25 mg weekly) (oral/injected) 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.

WEIGHT
7. Body weight ≥45 kg.

SEX
8. 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.

INFORMED CONSENT
9. Capable of giving signed informed consent as described in Section 7.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

OTHER SAFETY-RELATED
10. 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). 11. D_{LCO} ≥60%[a] predicted; FEV1 ≥70% predicted. a. For subjects with DLCO values ≥60% - <70%, a baseline chest high-resolution computed tomography (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. 12. No evidence of active or latent infection with 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 at screening defined as: i. A negative QuantiFERON Gold test or T-spot test (two 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 *Bacillus Calmette-Guérin* (BCG) vaccination be tested with QuantiFERON gold test). c. Chest X-ray within 12 weeks of Day 1 with no evidence of current or previous pulmonary tuberculosis, locally read by a radiologist. 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.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Pregnant or lactating, or women planning to become pregnant or initiating breastfeeding.
2. History of other inflammatory rheumatologic 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 (in the opinion of the investigator) persistent cough or clinically significant or unstable dyspnea that is unexplained.
5. QT interval corrected for heart rate (QTc) >450msec or QTc >480 msec 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 New York Heart Association 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, endocrinologic 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 at screening.
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 has required management of acute or chronic infections, as follows:

    a. Currently taking any suppressive therapy for a chronic infection (such as TB, 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 intramuscular (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. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but is not limited to:

    a. Intracranial aneurysm clips (except Sugita) or other metallic objects.

    b. History of intra-orbital metal fragments that have not been removed by a medical professional.

    c. Pacemakers or other implanted cardiac rhythm management devices and non-MR compatible heart valves.

    d. Inner ear implants.

    e. History of claustrophobia which may impact participation.

    f. History of sensitivity to Gd-containing contrast agents.

CONCOMITANT MEDICATIONS
17. Use of prohibited medications: Prior to AND throughout the study: • Any conventional DMARDs other than MTX (including hydroxychloroquine, sulphasalazine, minocycline, cyclosporin) must be withdrawn at least 2 weeks prior to Day 1.

- Subjects may require longer to discontinue leflunomide 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 must be obtained prior to beginning the screening period. However, other screening assessments, other than consent, must occur within 42 days prior to randomization.

- Azathioprine must be discontinued ≥28 days prior to randomization.
- Any alkylating agents (such as cyclophosphamide or chlorambucil).
- Plasmapheresis or intravenous immunoglobulin (IVIG) or use of Staph protein A column (Prosorba) within 26 weeks of Day 1.
- Biologic agents - all must be discontinued prior to Day 1:
  - anakinra or etanercept (4 weeks prior);
  - adalimumab (6 weeks prior);
  - infliximab (8 weeks prior);
  - certolizumab pegol or golimumab (10 weeks prior);
  - abatacept or tocilizumab (12 weeks prior);
  - belimumab, rituximab, or other selective B lymphocyte depleting agents (1 year prior, and if CD19/20+ counts are normal by fluorescence-activated cell sorter (FACS) analysis).

18. Tofacitinib must be discontinued at least 2 weeks prior to Day 1.

19. Corticosteroids:

- Any IM, IV or intra-articular (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).

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

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

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

RELEVANT HABITS
22. 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.

CONTRAINDICATIONS
23. 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.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
24. Abnormal chest X-ray within 12 weeks of Day 1 (locally read and reported by a radiologist) judged by the investigator as clinically-significant. 25. Any Grade 3 or 4 hematology or clinical chemistry laboratory abnormality (common terminology criteria for adverse events [CTCAE], 2009 v4.0) at screening. 26. 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 at screening. Refer to Section 5.3.1 and Section 5.3.2. 27. 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 at screening: • Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded. 28. Hepatitis C: Positive test for Hepatitis C virus (HCV) antibody confirmed on a subsequent blood sample by RNA-polymerase chain reaction (PCR) assay at screening. • 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. 29. Positive serology for HIV 1 or 2 at screening.

5.3. Screening/Baseline/Run-in 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 information about potential subjects who failed screening is required including demography, screen failure details, eligibility criteria, and SAEs.

5.3.1. Re-Screening

If a subject has not met all of the Eligibility Criteria within the 42-day screening period, re-screening is permitted. Subjects are only allowed to be re-screened once; the entire screening process must be repeated.

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

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

5.3.2.2. Pulmonary Function Tests

It is permitted to repeat the pulmonary function testing sessions (spirometry and/or D_{LCO}) once within the screening period, *i.e.* subjects may undergo a total of two D_{LCO} tests during the screening period).

If the screening D_{LCO} result is ≥60% but <70% predicted, a chest HRCT must be performed. If this cannot be done within the screening window, then the subject must be re-screened.

5.3.2.3. Electrocardiogram (ECG) Test

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). The QTc should be based on average QTc values of triplicate ECGs obtained over a brief recording period (*e.g.*, 5-10 minutes).

The triplicate electrocardiogram (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, three 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".

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, behavioral or administrative reasons. 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.

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 (refer to Section 4.6.1).
- 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.

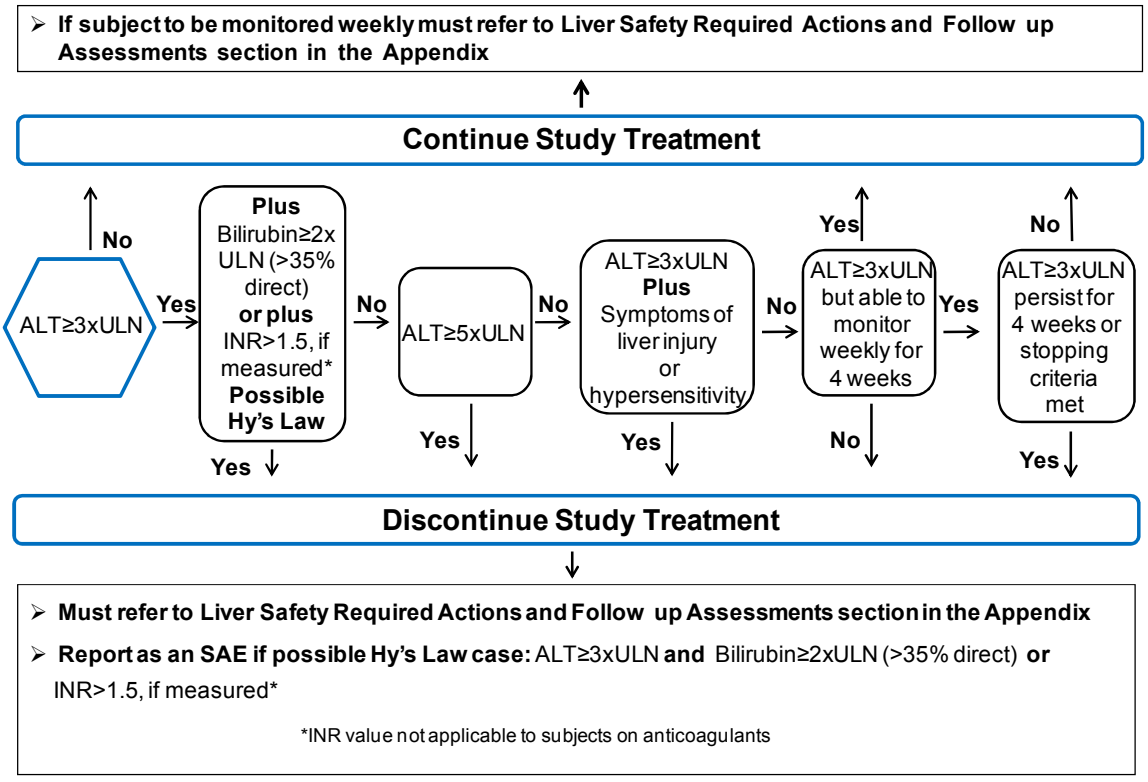
If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

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 Food and Drug Administration (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

The same QT correction formula must be used for each individual subject to determine eligibility for and discontinuation from the study. The QTc correction formula to be used is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). This formula may not be changed or substituted once the subject has been enrolled.

For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.

Once the QT correction formula has been chosen for a subject's eligibility, the same formula must continue to be used for that subject for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.

The QTc should be based on a single QTc value. The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

- The ECG may be repeated in triplicate if the recorded QTcF value is out of range. The QTc should then be based on averaged QTc values of the triplicate ECGs obtained over a brief recording period (*e.g.*, 5-10 minutes).

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 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 cough (common terminology criteria (CTC) grade 2 or 3) or dyspnea (Borg scale grade 3 or above) for three consecutive weeks. Details on CTC and Borg scale are provided in the SRM.

The subject should be referred to a pulmonologist for further assessment. The study drug should be suspended until the symptoms or signs that caused the 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 hematological 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 ≥two sequential tests), or occur recurrently (on two 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 (study treatment)	Control	Background treatment (started prior to and maintained during the study).
Formulation description:	See IB (GSK Document Number 2014N190256_01) for details.	Sterile 0.9% (weight/volume [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.

	Study Treatment		Co-medication
Dosage levels (volumes):	180 mg (1.2mL)	1.2 mL	MTX:7.5-25 mg/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). [Refer to Inclusion criterion 6 in Section 5.1.]
Route of Administration:	Study treatment 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
Dosing instructions:	GSK3196165/placebo should be administered on the same day each week ± 1 day for the first five weekly doses (with a minimum of 5 days between doses, for no more than two consecutive doses). Following this GSK3196165/placebo should be administered on the same day every other week (EOW) ± 3 days (with a minimum of 8 days between doses). Every attempt should be made to ensure all doses are administered.		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.	See label for details.
Method for individualizing dosage:	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 1.2 mL will be drawn into a small (*e.g.* 2 or 3 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 at the entry into study (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 electronic case report form (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 (GSK3196165 or placebo) 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

No dose adjustments are planned for this study.

6.4. Blinding

This will be a double-blind study, which means that the investigator and trial staff at the site (apart from the unblinded administrator [study coordinator or nurse], subject and sponsor personnel will be blinded to the study medication allocated to each individual subject.

There will be an unblinded administrator (study coordinator or nurse) that will prepare and administer the study medication. The barrel of the syringe will be shielded during investigational product administration so that subjects are not able to see any difference in the color between GSK3196165 and placebo.

The following will apply:

- 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. Unblinding will be done via IRTS; as described in the SRM.
- 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 case report form (CRF)

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 CRF.

- GSK's Global Clinical Safety and Pharmacovigilance 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.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. 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 coordinator 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/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.

6.7. Compliance with Study Treatment Administration

GSK3196165 or placebo will be administered by subcutaneous injection to subjects at the site by the unblinded administrator (study coordinator 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.

6.8. Treatment of Study Treatment Overdose

6.8.1. Overdose of GSK3196165

There is very limited clinical safety data for GSK3196165 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 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 study treatment 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 3 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.

6.8.2. 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 mucosal, hematological and gastrointestinal reactions. Leucovorin (IV) or folinic acid (oral) are specific antidotes for MTX and, following accidental over dosage, should be administered as soon as possible after the over dosage occurs, as the longer the delay in initiation of leucovorin or folinic acid, the less the effectiveness in counteracting the MTX toxicity. A dosage equal to, or greater than the MTX dose, should be given; 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 alkalization 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 dialyzer.

6.9. 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.

6.10. Concomitant Medications and Non-Drug Therapies

During the past decade, the ability of pro-inflammatory cytokines to alter the expression and activity of drug metabolizing enzymes has become increasingly evident [Lee, 2010; Zhou, 2011; Evers, 2013]. During inflammation, enzymes such as cytochrome P (CYP)450 can be downregulated leading to instances of reduced clearance and increased plasma concentrations of administered drugs. The administration of GSK3196165 can potentially alter circulating cytokine levels in a subject whose cytokine levels have been elevated previously. 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. The effect of GSK3196165 on CYP450 enzyme activity may persist for several weeks after stopping therapy.

6.10.1. Permitted Medications and Non-Drug Therapies

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

6.10.1.1. Corticosteroids

6.10.1.1.1. 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 study. Dose reductions 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 study treatment 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.

6.10.1.1.2. NSAIDs

Continued use of a single NSAID (including cyclo-oxygenase [Cox]-2 inhibitors) (*e.g.* diclofenac, ibuprofen, naproxen, celecoxib) is permitted 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 (date and time of use, number and strength of doses taken). However, subjects should be advised not to take any NSAIDs for breakthrough pain within 12 hours prior to an efficacy assessment visit.

6.10.1.1.3. Analgesics

Regular use of codeine, opium alkaloid, paracetamol/acetaminophen, propoxyphene, and tramadol is permitted in daily doses up to the maximum recommended according to locally accepted clinical practices. If, at the time of screening 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.

6.10.1.1.4. DMARD/Biologic Rescue Medications

The subject's disease will be assessed regularly throughout the study (as shown in Section 7.1). Rescue with DMARDs / biologics is not allowed in this study.

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.

6.10.2. Prohibited Medications and Non-Drug Therapies

Prohibited medications and non-drug therapies are described in Exclusion Criteria 13 through 21 in Section 5.2. Additional requirements are detailed in Section 6.10.2.1, Section 6.10.2.2, and Section 6.10.2.3.

6.10.2.1. Related to the Study

- IA corticosteroids are strongly discouraged within 8 weeks prior to Day 1, and then through Week 12.
- However, IA corticosteroids may be used in a limited fashion as treatment for severe RA flares.
- No more than 1 joint should be injected, during the study and the total dose of IA corticosteroid should not exceed 40 mg of triamcinolone (or equivalent) during the 12-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.

6.10.2.2. 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 metabolized 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.

6.10.2.3. 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

Procedures	Screening - up to 6 weeks	Base-line	Treatment Period								FU	EW[1]
			Week									
			1	2	3	4	6	8	10	12	22	
	Visit											
	1	2	3	4	5	6	7	8	9	10	11	
	Day											
		1	8	15	22	29	43	57	71	85	155	
Written Informed Consent(s)	X											
Subject Demography	X											
Medical, Disease, Therapy History	X											
Inclusion/Exclusion Criteria	X											
PRO[2] and efficacy assessments[3]												
Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis[2]	X	X[4]	X	X	X	X	X	X	X	X	X	X
HAQ-DI[2]	X	X[4]	X	X	X	X	X	X	X	X	X	X
RA Symptom and Impact Diary[2]	X	X[4]	X				X			X	X	X
Swollen (66) & Tender (68) Joint Count[3]	X	X[4]	X	X	X	X	X	X	X	X	X	X
MRI	X[20]					X[21]				X[21]	X[21]	X[22]
Safety Evaluations[5]												
Concomitant Medication	X	X[4]	X	X	X	X	X	X	X	X	X	X
Physical Examination[6]	X	X[4]								X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[7]	X									X		X
AEs/SAEs[8]	X	X	X	X	X	X	X	X	X	X	X	X
Cough, Lung Auscultation, Pulse Oximetry, Borg Dyspnea Scale	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray[9]	X											
Spirometry (FEV1, FVC), D_{LCO}	X[10]									X[11]	X[11]	X[11]

Procedures	Screening - up to 6 weeks	Base-line	Treatment Period								FU	EW[1]
			Week									
			1	2	3	4	6	8	10	12	22	
	Visit											
	1	2	3	4	5	6	7	8	9	10	11	
	Day											
		1	8	15	22	29	43	57	71	85	155	
Laboratory Assessments												
Hematology, Chemistry	X	X[4]		X		X		X		X	X	X
TB, HBsAg, HepB cAb, HepC Ab, HIV	X											
CRP, ESR[12]	X	X[4]	X	X	X	X	X	X	X	X	X	X
RF, ACPA (anti-CCP)		X[4]										
Cholesterol, triglycerides, HDL, LDL[13]		X[4]								X	X	X
Pregnancy test[14]	S	U				U		U		U	U	U
Urinalysis (dip stick)	X					X		X		X	X	X
Other Laboratory Assessments												
PK Sampling (GSK3196165)[15]		X	X	X		X	X	X		X	X	X
GM-CSF & PD blood biomarkers	X	X[4]	X	X		X	X	X		X	X	X
Whole blood flow cytometry		X[4]	X			X				X	X	X
RNA		X[4]								X	X	X
PGx sampling DNA[16]		X[4]										
Lung biomarkers[17]		X[4]								X	X	X
Anti-GM-CSF auto-antibodies[17]		X[4]										
Immunogenicity[18]		X[4]		X		X				X	X	X
Study Treatment GSK3196165/placebo[19] (Methotrexate and folic acid weekly throughout treatment with GSK3196165)		X	X	X	X	X	X	X	X			

Abbreviations: ACPA=anti-cyclic citrullinated protein antibody; AE=adverse event; CCP=cyclic citrullinated peptide; CRP=C-reactive protein; DNA=deoxyribonucleic acid; D_{LCO}=diffusing capacity of the lung for carbon monoxide; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; EW=early withdrawal; FEV1=forced expiratory volume in one second; FU=follow-up; FVC=forced vital capacity; GM-CSF=granulocyte-macrophage colony-stimulating factor; HAQ-DI=Health Assessment Questionnaire Disability Index; HDL=high density lipoprotein; HBsAg=hepatitis B surface antigen; HepB cAb=anti-hepatitis B core antibody; HepC Ab=hepatitis C virus antibody; HIV=human immunodeficiency virus; LDL=low density lipoprotein; MRI=magnetic resonance imaging; PD=pharmacodynamic; PGx=pharmacogenomic; PK=Pharmacokinetic; PRO=patient reported outcome; RA=rheumatoid arthritis; RF=rheumatoid factor; RNA=ribonucleic acid; S=serum; SAE=serious adverse event; TB=*Mycobacterium tuberculosis*; U=urine.

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. All patient reported outcome (PRO) assessments should be conducted before any tests, procedures, assessments or consultations, to avoid influencing the subjects' perception.
3. The same individual (where possible) should perform all disease assessments for an individual subject (with separate joint assessor).
4. Assessments may be performed up to 24h before dosing.
5. All safety evaluations should be conducted before dosing.
6. Brief physical examination (assessments of the skin, lungs, CV system, and abdomen [liver and spleen]) at visits after screening.
7. Electrocardiogram (ECG) should be performed before vital signs, blood draws and dosing (triplicate ECGs required at screening, and single thereafter unless there are safety concerns, in which case repeats may be required (see Section 7.6.10)).
8. AEs/SAEs reported from start of study medication until the last follow-up visit. 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.
9. Unless performed within previous 12 weeks (no repeat if subject re-screened).
10. If D_{LCO} ≥60% but <70% predicted, a chest HRCT must be performed. If this cannot be done within the screening window, then the subject must be re-screened.
11. Consider repeat D_{LCO} if >15% relative decrease from baseline (recommendations provided in the Pulmonary Safety Guidance document).
12. ESR measured locally.
13. >8h fasting required before blood draw.
14. For women of child-bearing potential. S=serum; U=urine.
15. Blood samples taken before dosing.
16. In consenting subjects.
17. To be analyzed at end of study or in event of pulmonary safety signal.
18. In addition to these scheduled immunogenicity assessments, "event-driven" testing (see Section 7.8) 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.
19. 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 every other week (EOW) ±3 days.
20. Subjects must have passed all screening assessments, including laboratory tests, prior to undertaking MRI scanning.
21. MRI may be performed up to 7 days after scheduled visit.
22. MRI should be performed at Early Withdrawal visit if previous MRI was done >14 days before.

7.2. Screening and Critical Baseline Assessments

After written, informed consent (including separate consent for genetics), 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 42 days of Day 1 (except for subjects being treated with leflunomide, where written informed consent for the 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. This list does not apply to subjects 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.

- The following demographic parameters will be captured at screening: year of birth, sex, race and ethnicity.
- Medical/medication/family history will be assessed at screening, 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.
- RA history – disease and symptom duration, medication history, RA functional class (I, II or III).
- Physical examination (complete examination at screening, and brief examination at baseline; see Section 7.6.8).
- Vital signs including temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate, measured in semi-supine position.
- Triplicate 12-lead ECG (before blood samples are taken) (screening only).
- Chest X-ray (screening only).
- Spirometry FEV1, FVC, and D_{LCO} (PFTs performed according to 2005 ATS/ERS recommendations, see Section 5.3.2.2 and SRM for additional details) (screening only).
- Cough, Lung Auscultation, Pulse Oximetry, Borg Dyspnea.
- AE reporting and recording of concomitant medication.
- Blood samples for:
    - Hematology (full/complete blood count and differential).
    - Biochemistry.
    - Whole blood flow cytometry (baseline only).
    - Serum beta subunit human chorionic gonadotropin (βhCG) pregnancy test (screening only).

  - HIV antibody, HBsAg, anti-hepatitis B core antibody (anti-HepBc Ab), and HepC Ab testing (screening only).
  - CRP.
  - ESR.
  - Cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) (baseline only).
  - Autoimmune serology: RF and ACPA (*i.e.*, anti- cyclic citrullinated peptide [CCP] antibodies) (baseline only).
  - QuantiFERON Gold or T-spot test for TB (If unavailable/unapproved, then tuberculin skin test is permitted) (screening only).
  - Exploratory GM-CSF and pharmacodynamic (PD) blood biomarkers and lung biomarkers and anti-GM-CSF auto-antibodies (baseline only).
  - PK samples and immunogenicity (baseline only).
  - RNA (baseline only).
  - Pharmacogenomic DNA (in consenting subjects) (baseline only).
- Urine sample for:
  - Routine urinalysis (screening only).
  - Urine βhCG pregnancy test (baseline only).
- Disease activity assessments (see Section 7.5)
  - Tender joint count (68 joints).
  - Swollen joint count (66 joints).
  - Patient's Assessment of Arthritis Pain.
  - Patient's Global Assessment of Arthritis (PtGA).
  - Physician's Global Assessment of Arthritis (PhGA).
  - Health Assessment Questionnaire Disability Index (HAQ-DI).
  - MRI (screening only).
- Patient-reported outcome (PRO) questionnaires (see Section 7.11)
  - RA Symptom and Impact Diary.

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

7.3.1. Exploratory 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 analyzed pre- and post-GSK3196165. In addition blood samples will be collected and may be analyzed for markers which may be predictive of lung damage. 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.

7.3.2. Biomarkers

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

- Target engagement (TE): analysis of free soluble GM-CSF and soluble GM-CSF complexed to GSK3196165.
- Effects of GSK3196165 on target cell populations: may include, but not limited to, circulating levels of T, B, NK, Th17, T regulatory cells and activated monocytes, dendritic cells, neutrophils.
- Biomarkers which may be indicative of RA disease activity: may include, but not limited to 14-3-3η, ACPA, CRP, and RF.
- Soluble biomarkers which may be predictive of response to GSK3196165 such as C1M, C2M, C3M, CRPM, VICM, MRP8/14, MMP-3, and 14-3-3η.
- Pharmacodynamic biomarkers to assess response to GSK3196165 such as IL-1β, TNFα, IL-6, IL-8, IL15, IL-23 and IL-17A/F, and chemokines such as CCL17, CXCL4, CXCL7, CXCL13, CCL22; and complement proteins such as C5a, ratio C3/C3dg, TCC, C4, C4a, sCD163.
- Biomarkers of extracellular matrix (ECM) or aggrecan degradation (e.g. may include, but not limited to, YKL 40, ARGS neoepitope).

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

- Whole blood RNA markers of GM-CSF/macrophage signaling and response to GSK3196165.
- Whole blood DNA analysis to explore the relationship between genetic variants in the host and response to GSK3196165.

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

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

7.3.3. Target Engagement (TE)

If data permits, a PK/TE modeling analysis will be conducted. This modeling work will be detailed in the reporting and analysis plan (RAP).

The rationale for the selection of timepoints is:

- Baseline: to measure PK and target engagement (± potential biomarkers status) at baseline.
- Week 1 and Week 2: to characterize the increase in PK and target engagement (± activation of potential biomarkers) due to the loading phase.
- Week 4: to measure target engagement (± biomarkers) at the maximum plasma concentration.
- Week 6 and Week 8: to measure if a maintenance regimen administered every two weeks can maintain sufficient target engagement (± activation of potential biomarkers) at steady state.
- Week 12 and Week 22: to assess the decline in PK and target engagement after the last dose.

7.4. 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 AEs.

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

7.5. Clinical Efficacy

7.5.1. Magnetic Resonance Imaging

The most affected hand will be documented at screening and used for all imaging visits. If subjects report both hands are equally involved, then the subject's dominant hand will be used. Each subject's most affected hand/wrist will be imaged by MRI at Screening, Week 4, Week 12 and Week 22 (see Section 7.1, Time and Events Schedule). The scanning protocol will include routine localizers, T1 measurement sequences, dynamic DCE-MRI acquisition, and acquisitions required for OMERACT RAMRIS and RAMRIQ scoring.

The following will be assessed:

- Change from baseline in synovitis, osteitis and erosion as assessed OMERACT RAMRIS and RAMRIQ in the hand/wrist.
- Change from baseline in joint inflammation as measured by DCE-MRI in the hand/wrist:
  - K^{trans}.
  - $V_{e.}$
  - $V_{p.}$
  - IRE.
  - ME.

7.5.2. Clinical assessments

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, visual analogue scale (VAS) (global disease) for the subject and treating physician, 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 7.11 and laboratory assessments (CRP). Based on these assessments ACR (20, 50 and 70), DAS28(CRP) and the EULAR response will be calculated.

RA symptoms will be assessed through the subject completion of an RA Symptom and Impact Diary (see Section 7.11.2).

7.5.3. Joint Assessments

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

7.5.3.1. 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.

7.5.3.2. Independent Joint Evaluator

One or more independent assessors, who have documented experience in performing joint assessments, will be designated at each study site to perform joint assessments. Preferably the same independent assessor will perform all joint assessment for the same subject throughout the study. 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 study.

The independent joint assessor should have no other contact with the subject during the study, 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.

7.5.4. Patient's Assessment of Arthritis Pain

Subjects will assess the severity of their current arthritis pain using a 100 unit 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.

7.5.5. Patient's Global Assessment of Arthritis

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

Further details of this assessment are provided in the SRM.

7.5.6. Physician's Global Assessment of Arthritis

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

Further details of this assessment are provided in the SRM.

7.5.7. 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 time point.

The components of the DAS28 arthritis assessment include:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- CRP or ESR.
- PtGA.

7.5.8. ACR Assessments

The ACR'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 time point.

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.
- PtGA.
- PhGA.
- CRP or ESR.
- HAQ-DI.

7.6. Safety

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

7.6.1. Screening Visits

- Chest X-ray (posterior to anterior [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% - <70%, and it is recommended that the subject will be reviewed by a local pulmonologist to exclude significant pre-existing respiratory disease.
- Immunogenicity testing.

7.6.2. 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 AEs, 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.

7.6.3. 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, lactate dehydrogenase [LDH], cholestenoic acid).
- ECG measurements.
- Vital signs.
- Hematological and clinical chemistry parameters.
- Physical examinations.
- Pregnancy test (for women of child-bearing potential).

7.6.4. 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.

7.6.4.1. 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 study medication), at the time points 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.

7.6.4.2. 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

7.6.4.3. 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 4.6.1) 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.

7.6.4.4. Cardiovascular and Death Events

For any cardiovascular (CV) events detailed in Appendix 12.4 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the CRF within 1 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 1 week of when the death is reported.

Investigators will be required to fill out event specific data collection tools for CV AEs and SAEs detailed in Section 12.4.4, Appendix 12.4. This information should be recorded in the specific cardiovascular eCRF within 1 week of when the AE/SAE(s) are first reported.

7.6.5. 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 judgment 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.

7.6.6. Adverse Events of Special Interest

Please see Section 4.6.1 for a discussion of potential risks with GSK3196165. AEs of special interest include:

- Serious infections, including serious respiratory infections and TB.
- Opportunistic infections.

- Neutropenia (grade 3 or 4).
- Respiratory events including:
  - Persistent (for 3 consecutive weeks) reduction in D_{LCO} >15%
  - Persistent (for 3 consecutive weeks) cough and/or dyspnea
  - Non-life-threatening pulmonary changes related to surfactant accumulation.
- PAP.
- Hypersensitivity reactions, including anaphylaxis.
- Injection site reactions.
- Persistent cough or dyspnea.

7.6.6.1. 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 requires 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.

7.6.6.2. 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_01and will notify the IRB/IEC, if appropriate according to local requirements.

7.6.7. 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.

7.6.8. Physical Exams

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

7.6.9. 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.

7.6.10. Electrocardiogram

See Section 5.2 regarding QTc exclusion criteria.

Single 12-lead ECGs will be obtained (before dosing, vital signs measurements and blood samples taken) at the time points after Day 1 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. The ECG may be repeated in triplicate if the recorded QTcF value is out of range. The QTc should then be based on averaged QTc values of the triplicate ECGs obtained over a brief recording period (*e.g.*, 5-10 minutes). Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.6.11. 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/center 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 any locally performed 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 Protocol Required Safety Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hemoglobin Hematocrit Mean cell volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Erythrocyte count Reticulocyte count Leukocyte count Leukocyte differential count neutrophils	Sodium Potassium Calcium Phosphate Urea Creatinine Creatinine clearance (calculated) AST ALT γ-glutamyl transpeptidase	**Urine dipstick** Glucose Protein Microscopy of urine sediment for erythrocytes, leukocytes and casts if urine dipstick abnormal

Hematology	Biochemistry	Urinalysis
eosinophils basophils monocytes lymphocytes Platelets Activated partial thromboplastin time (aPTT) Prothrombin Time (PT) International Normalized Ratio (INR) Fibrinogen ESR*	(GGT) LDH Alkaline phosphatase (AP) Bilirubin (total) Creatine Phosphokinase (CPK) Total protein Albumin Albumin/globulin ratio Serum Glucose CRP Cholesterol** Triglycerides** HDL** 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 7.3.2). Baseline measurement of GM-CSF autoantibodies will be measured.

7.6.12. 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.
- PFTs – spirometry (FEV1, FVC), gas transfer (D_{LCO}).

PFTs should be performed according to 2005 ATS/ERS recommendations for lung function testing [MacIntyre, 2005; Miller, 2005a; Miller, 2005b]. Spirometry should be

performed prior to D_{LCO} testing. The standards for acceptable testing sessions are described further in the Pulmonary Safety Guidance document in the SRM.

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 treatment 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 SRT may request copies of any reports or images for central review.

7.7. Pharmacokinetics

Details of PK blood sample collection, processing, storage and shipping procedures are provided in the central laboratory manual.

7.7.1. Blood Sample Collection

Blood samples for PK analysis of GSK3196165 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection 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.

7.7.2. 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).

7.8. 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 anti-drug antibodies (ADAs). 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 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.

7.9. Magnetic Resonance Imaging

Each subject's most affected wrist (corresponding to the affected hand which is determined and documented at screening) will be imaged by MRI at Screening, Week 4, Week 12 and Week 22 (see Section 7.1). If a scanning failure occurs at any visit, if feasible a rescan is allowed within 7 days after the failed scan after consultation and agreement with the Medical Monitor. There will be a minimum of 24 hours between scans where gadolinium (Gd) contrast is used. The MRI will be used in order to non-invasively quantify the degree of inflammation and structural changes within the target joint.

Each MRI total scan time should not exceed 1 hour. For each subject, MRIs must be performed on the same scanner and using the same type of chelated Gd contrast agent as was used at screening. If scanning cannot occur on the same scanner within the visit time window due to hardware failure, an alternate scanner may be used or the time window may be extended by 3 days only after consultation and agreement with the Medical Monitor.

On attendance at the MRI department, subjects will be placed in the scanner and will be prepared for intravenous contrast agent administration. The scanning protocol will include routine localizers, T1 measurement sequences, DCE-MRI acquisition, and acquisitions required for OMERACT RAMRIS and RAMRIQ scoring. Additional exploratory MRI endpoints, as detailed in the Imaging Acquisition Manual, may also be acquired for exploratory purposes.

Details of scanning site training procedures, acceptable Gd contrast agents, and scanning protocols will be provided in a dedicated Imaging Acquisition Manual.

All MRI scans will be available at site, and may be reported at the site by a radiologist (non-anonymized) for clinical abnormalities per local standard procedures.

7.10. Genetics

Information regarding genetic research is included in Appendix 12.6.

7.11. 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.

7.11.1. Health Assessment Questionnaire – Disability Index (HAQ-DI)

The functional status of the subject will be assessed by means of the 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.

7.11.2. Rheumatoid Arthritis Symptoms and Impact Diary PRO

Symptoms associated with RA will be assessed using a novel RA Symptom and Impact Diary, as per the Time and Events Schedule (Section 7.1).

8. DATA MANAGEMENT

- For this study, subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, *e.g.*, removing errors and inconsistencies in the data.
- 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. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

No formal hypotheses are to be tested. Differences between the treatment groups for the MRI synovitis data will be assessed by deriving the 95% credible interval. The analysis will be performed in a Bayesian framework, making use of historical data on the placebo arm where appropriate. The posterior distribution of the treatment difference will be computed, conditional on the observed data and the assumed prior distribution and the 95% credible interval will be derived from the posterior distribution.

For all other endpoints, differences between the treatment groups will be assessed using 95% confidence intervals (CIs). Historical data may be used where available.

9.2. Sample Size Considerations

The sample size for this study is based on feasibility.

9.2.1. Sample Size Assumptions

For the MRI synovitis data, based on a review of results in the literature, the standard deviation (SD) for both treatment groups is assumed to have a value of 2.5. Based on this value, assuming prior information cannot be used, with 30 subjects on GSK3196165 180 mg and 10 subjects on placebo, aiming for 50% early and 50% established RA subjects, it is estimated that the lower and upper bounds of the 95% CI for the difference would be within 1.8 points of the difference. This is considered the worst case precision and further estimates assuming different weights for the prior distribution on placebo will be assessed to estimate any improvement in the precision of the CI.

9.2.2. Sample Size Sensitivity

Not applicable.

9.2.3. Sample Size Re-estimation or Adjustment

Not applicable.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The primary population will be the Intent-to-Treat (ITT) population, defined as all subjects who were randomized to treatment and who received at least one dose of study treatment.

9.3.2. Final Analysis

The final analysis will be conducted when all subjects have completed their last follow up visit.

9.3.3. Interim Analysis

No interim analysis is planned for this study.

9.4. Key Elements of Analysis Plan

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

For the MRI data, the primary analysis will be a repeated measures Bayesian model for the difference between treatments over each visit. The full details of this approach will be provided in the analysis plan.

The data will be analyzed across all subjects, and may also be presented for each disease duration subgroup (stratification factor).

For other continuous endpoints Bayesian and frequentist methods will be used as appropriate.

In addition, the relationship between the mechanistic / biomarker endpoints and clinical effects (*e.g.*, ACR20 Response) will be graphically presented and analyzed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic / biomarker effect significantly explains or predicts the effect on the clinical endpoints. This may be conducted through comparing statistical models; incorporating different explanatory terms (*i.e.*, mechanistic / biomarker endpoints) with the 'null' model (no mechanistic / biomarker endpoints); or, if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed.

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

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 or designee will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (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 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.
- Obtaining signed informed consent.
- Investigator reporting requirements (*e.g.* reporting of AEs/SAEs/protocol deviations to IRB/IEC).
- GSK or designee will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study.
- 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.

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12. APPENDICES

12.1. Appendix 12.1 – Abbreviations and Trademarks

Abbreviations

µg	micrograms
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
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AMD	Age-related macular degeneration
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATS	American Thoracic Society
AUC	Area under the plasma concentration time curve
$AUC_{(0-168)}$	Area under drug concentration time curve from time zero to 168 hours postdose
$AUC_{(0-336)}$	Area under drug concentration time curve from time zero to 336 hours postdose
βhCG	Beta-subunit human chorionic gonadotropin
BCG	*Bacillus Calmette-Guérin*
C1M	MMP-2,9,13-degraded type I collagen
C2M	MMP-degraded type II collagen
C3	Complement component 3
C3dg	Complement component 3dg
C3M	MMP-9-degraded type III collagen
C4	Complement component 4
C4a	Complement component 4a
C5a	Complement component 5a
CCL17	Chemokine (C-C Motif) Ligand 17
CCL22	Chemokine (C-C Motif) Ligand 22
CCP	Cyclic citrullinated peptide
CD4	Cluster of differentiation antigen 4
CD19/20	Cluster of differentiation antigen 19/20
CD68	Cluster of differentiation antigen 68
CI	Confidence interval
CIA	Collagen-induced arthritis
Cl_{IV}/Cl_{SC}	Intravenous plasma clearance/subcutaneous plasma clearance
COPD	Chronic obstructive pulmonary disease
Cox	Cyclo-oxygenase

CPK	Creatine phosphokinase
CRO	Contract Research Organization
CRF	Case report form
CRP	C-reactive protein
CRPM	MMP-degraded CRP
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse events
CV	Cardiovascular
CXCL4	Chemokine (C-X-C Motif) Ligand 4
CXCL7	Chemokine (C-X-C Motif) Ligand 7
CXCL13	Chemokine (C-X-C Motif) Ligand 13
CYP450	Cytochrome P450
DAS	Disease activity score
DAS28	Disease activity score for 28 different joints
DAS28(CRP)	Disease activity score for 28 different joints with CRP value
DCE-MRI	Dynamic contrast enhanced magnetic resonance imaging
dL	Deciliter
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
DMARD	Disease modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
DRE	Disease-related event
ECG	Electrocardiogram
ECM	Extracellular matrix
eCRF	Electronic case report form
EOW	Every other week
ePRO	Electronic patient reported outcome
ERS	European Respiratory Society
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EW	Early withdrawal
FACS	Fluorescence-activated cell sorter
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FRP	Females of reproductive potential
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd	Gadolinium
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSK	GlaxoSmithKline
h	Hour
HAQ-DI	Health Assessment Questionnaire Disability Index

HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HepB cAb	Anti-hepatitis B core antibody
HepC Ab	Hepatitis C virus antibody
HC gp	Human cartilage glycoprotein
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
HRT	Hormone replacement therapy
IA	Intra-articular
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IL-1	Interleukin 1
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-12p70	Interleukin 12p70
IL-15	Interleukin 15
IL-17A/F	Interleukin 17A/F
IL-23	Interleukin 23
IM	Intramuscular
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRE	Initial rate of enhancement
IRTS	Interactive response technology system
ITT	Intent-to-Treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
Kg	Kilogram
KL-6	Krebs von den Lungen-6
K^{trans}	Exchange rate
L	Litre
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume
ME	Maximal signal intensity enhancement

MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHC	Major histocompatibility complex
mL	Milliliter
Mmol	millimole
MMP-3	Matrix metalloproteinase 3
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRP	Myeloid-related protein
msec	millisecond
MTX	Methotrexate
MTX-IR	Methotrexate-inadequate response
N	Number of subjects
NB	Nota bene
NK	Natural killer
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NSAID	Non-steroidal anti-inflammatory drug
NSF	Nephrogenic systemic fibrosis
OMERACT	Outcome Measures in Rheumatology
PA	Posterior to anterior
PAP	Pulmonary alveolar proteinosis
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFT	Pulmonary function test
PGx	Pharmacogenomic
PtGA	Patient's Global Assessment of Arthritis
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
PT	Prothrombin Time
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QW	Once a week
RA	Rheumatoid arthritis
RAMRIQ	Rheumatoid arthritis MRI quantitative score
RAMRIS	Rheumatoid arthritis MRI scoring system
RAP	Reporting and Analysis Plan
RF	Rheumatoid factor
RNA	Ribonucleic acid
SAA	Serum amyloid A
SAE	Serious adverse event
SC	Subcutaneous
sCD163	Soluble cluster of differentiation 163 (scavenger receptor for hemoglobin-haptoglobin complex)
SD	Standard deviation

SP-D	Surfactant protein D
SRM	Study Reference Manual
SRT	Safety Review Team
TB	*Mycobacterium tuberculosis*
TCC	Terminal complement complex
TE	Target engagement
TEAE	Treatment emergent adverse event
Th17	T helper 17 cell
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor alpha
TST	Tuberculin skin test
ULN	Upper limit of normal
VAS	Visual analogue scale
V_e	Interstitial volume
VICM	Matrix metalloproteinase-degraded fragment of vimentin
V_p	Plasma volume
WBC	White blood count
w/v	Weight/volume
YKL-40	Serum chondrex

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

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

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
    - Oral Contraceptive, either combined or progestogen alone [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	• Viral hepatitis serology[4] • Blood sample for PK analysis, obtained less than 12 weeks after last dose[5] • Serum CPK and 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

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high performance liquid chromatography 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 computerized 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, stabilize 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 judgment 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 Contract Research Organization (CRO).
- Site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (*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 PK (absorption, distribution, metabolism, and elimination), or PD (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 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 Asp Med 2012; 33: 467-86.

12.7. Appendix 12.7: Important Study Assessment Details and 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, and safety assessments (AEs, 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 electronic patient reported outcome (ePRO) device. The subject will complete the Borg scale on paper and study personnel will enter the results into the eCRF.

12.8. Appendix 12.8 Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 12.9 - Protocol Changes

Protocol Amendment: 01 (applies to all countries)

Section 1. Protocol Synopsis for Study 205180 and Section 3. Objectives and Endpoints.

Classified primary and secondary objectives and endpoints.

Rationale

Previous version listed all objectives and endpoints as exploratory.

Section 1. Protocol Synopsis for Study 205180, Section 4.1. Overall Design, Section 5.3 .1. Re Screening, Section 7.1. Time and Events Table, and Section 7.2. Screening and Critical Baseline Assessments

Screening window extended to six weeks.

Rationale

To facilitate scheduling of screening MRI scan, which should only be performed after other screening assessments have been passed.

Section 4.3. Type and Number of Subjects

Estimated number of screened subjects revised.

Rationale

More conservative estimate based on recent clinical study experience.

Section 4.6.1. Risk Assessment

Deleted ">15% relative decrease in D_{LCO} from screening" as trigger for subject to be withdrawn from study drug.

Rationale

Second D_{LCO} test is at Week 12, after dosing of study drug has been completed.

Section 5.1. Inclusion Criteria, Section 5.3.2.2. D_{LCO} test, Section 7.1. Time and Events Table, Section 7.2. Screening and Critical Baseline Assessments, and Section 7.6.12. Pulmonary Assessments

Consolidated details of PFTs into additional guidance in Section 7.6.12.

Rationale

To avoid any misunderstanding of PFTs.

Section 5.1. Inclusion Criteria

Addition of Day 1 joint count, and clarification that chest HRCT must be performed if D_{LCO} ≥60% - <70% predicted.

Rationale

To ensure subjects still have active RA with the extended screening window, and to avoid any misunderstanding of requirement for chest HRCT.

Section 5.2. Exclusion Criteria

Addition of history of sensitivity to Gd-containing contrast agents.

Rationale

To maintain safety.

Section 5.3.1.Re-Screening

Re-screening is permitted.

Rationale

Had previously stated that re-screening is required.

Section 7.1. Time and Events Table

Revision that subjects must have passed all screening assessments, including laboratory tests, prior to undertaking MRI scanning, and that whole blood flow cytometry is scheduled at Baseline (Day 1).

Rationale

It is more appropriate that these tests are done for patients likely to be randomized.

Section 7.1. Time and Events Table and Section 7.2 Screening and Critical Baseline Assessments

Clarification that RNA analysis is not part of the pharmacogenetics substudy.

Rationale

RNA transcriptomics/sequencing is not proposed for this study.

Section 7.5.2. Clinical assessments

Removed “daily”.

Rationale

Error in frequency of assessment.

Section 7.9. Magnetic Resonance Imaging

Re-worded, to indicate that all MRI scans will be available at site, and may be reported locally.

Rationale

Local standard procedures for reporting MRI scans may differ.

Appendix 12.1. Abbreviations and Trademarks

Added missing abbreviations.

Rationale

Some abbreviations had not been included.

Appendix 12.2. Contraception Eligibility Criteria for Female and Male Subjects

Removed requirement for two forms of complementary contraception, except when using hormonal contraceptives.

Rationale

Due to potential drug interaction with CYP450 substrates, a second form of contraception is required for subjects using hormonal contraceptives. This requirement does not apply to subjects that are not using hormonal contraception, hence the contraception guidance has been corrected.

Appendix 12.7. Important Study Assessment Details and Study Specific Equipment

Removed “morning stiffness” assessment, and added that the Borg dyspnea scale will be completed on paper.

Rationale

Morning stiffness is not being recorded in the study, and an ePRO device not available for the Borg scale.