

## TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Protocol Amendment

<b>Title:</b>	A Phase 1/2, Double-Blind, Placebo-Controlled Study of the Pharmacokinetics, Safety and Tolerability of GSK3196165 in Combination with Methotrexate Therapy, in Japanese Subjects with Active Moderate-Severe Rheumatoid Arthritis Despite Treatment with Methotrexate.
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Revision contents: Change of Inclusion Criterion for CRP in Section 5.1.		

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- 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.

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# 1. PROTOCOL SYNOPSIS FOR STUDY 201789

## Rationale

Study 201789 is a Phase I/II study designed to provide the data necessary to assess the pharmacokinetics, safety and tolerability of GSK3196165 for 12 weeks treatment period, in combination with methotrexate (MTX) therapy, in Japanese subjects with active moderate-severe rheumatoid arthritis (RA) despite treatment with MTX. In addition, this study will assess efficacy of GSK3196165 in Japanese subjects.

## Objective(s)/Endpoint(s)

Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"> <li>To assess the pharmacokinetics of GSK3196165 in Japanese RA subjects</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacokinetic parameters of GSK3196165 calculated from sparse sampling concentrations</li> </ul>
<ul style="list-style-type: none"> <li>To assess the safety and tolerability of GSK3196165 in combination with MTX therapy in Japanese RA subjects</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of adverse events, serious adverse events and adverse events of special interest</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>To assess the safety other than primary endpoints</li> </ul>	<ul style="list-style-type: none"> <li>Vital signs, 12-lead ECG and laboratory assessment</li> <li>Immunogenicity (anti-GSK3196165 antibody)</li> </ul>
<ul style="list-style-type: none"> <li>To assess the efficacy in Japanese RA subjects</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in disease activity score for 28 different joints [DAS28(CRP)] at all assessment timepoints</li> </ul>

## Overall Design

- This is a randomized, double-blind, parallel group, 3 dosage level, placebo-controlled, Phase 1/2 study with the objective to assess pharmacokinetics (PK), safety, tolerability and efficacy of GSK3196165 for 12 weeks, in combination with MTX, in Japanese subjects with active moderate-severe RA despite treatment with MTX.
- Approximately 40 subjects will be randomized into the study (10 subjects in each treatment groups).

## Treatment Arms and Duration

This study is composed of up to 4 weeks screening period, 12 weeks treatment period (last dose Week 10), and 10 weeks follow-up period (12 weeks from last dose).

Subjects will be randomized (1:1:1:1) to placebo or one of three subcutaneous (SC) GSK3196165 doses at Day 1 (Week 0).

Treatment with GSK3196165 or placebo will be given weekly as a single SC injection by an unblinded administrator. There will be 5 weekly injections (Days 1, 8, 15, 22, 29), then every other week (EOW) injections at Days 43, 57 and 71 (Week 6, 8, 10, respectively).

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

### **Type and Number of Subjects**

Target population of this study is Japanese subjects with active moderate-severe RA who previously received oral MTX (at a dose between 8-16 mg/week for at least 12 weeks, with a stable and tolerated dose for  $\geq 4$  weeks).

Approximately 55 subjects will be screened to achieve 40 randomized subjects.

### **Analysis**

For serum concentrations of GSK3196165 over time, individual data will be listed and presented in graphical form, and summary statistics at each time point will be calculated by each dose level. The following PK variables after the last dosing will be derived as data allowed: maximum concentration (C<sub>max</sub>), time to maximum concentration (t<sub>max</sub>), area under the curve (AUC<sub>tau</sub>, AUC(0-inf)), and elimination half-life (t<sub>1/2</sub>). For PK parameters, summary statistics will be calculated by each dose level, and scatter plots against the dose level will be generated. Dose proportionality will also be assessed with the power model.

All adverse events will be coded using medical dictionary for regulatory activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of subjects with any adverse events will be summarized by dose. The study treatment-related AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be reported separately.

The ITT population with observed case dataset will be used for efficacy analyses. Time course of the change from baseline in DAS28(CRP) will be analyzed by mixed model for repeated measurements (MMRM). The dose response analyses will be performed on the change from baseline in DAS28(CRP) at Week 12.

## 2. INTRODUCTION

GSK3196165 is a recombinant human monoclonal antibody (mAb) targeting granulocyte-macrophage colony stimulating factor (GM-CSF) and is currently under development as a treatment for rheumatoid arthritis (RA) subjects with inadequate response to methotrexate (MTX).

### 2.1. Study Rationale

Study 201789 is a Phase I/II study designed to provide the data necessary to assess the pharmacokinetics (PK), safety and tolerability of GSK3196165 for 12 weeks treatment period, in combination with MTX therapy, in Japanese subjects with active moderate-severe RA despite treatment with MTX. In addition, this study will assess efficacy of GSK3196165 in Japanese subjects.

### 2.2. Brief Background

#### 2.2.1. Rheumatoid Arthritis

RA is a chronic, systemic inflammatory autoimmune disease, characterised by a symmetrical polyarthritis that is associated with substantial disability and morbidity. RA affects approximately 0.5-1.0% of the worldwide population (0.6-1.0% of Japanese population [Yamanaka, 2014]), 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 synthetic DMARDs (csDMARDs), of which MTX is the gold standard, and biological DMARDs which target cytokines (e.g. tumor necrosis factor [TNF]  $\alpha$ , interleukin [IL] -6) or T-cells. However, a substantial proportion of patients either fail to respond, or have inadequate response, to currently available RA therapies [Gaujoux-Viala, 2014; Nam, 2014]. Therefore, there is still a medical need for more effective treatments choices for RA with alternative mechanisms of action.

#### 2.2.2. GM-CSF and RA

Accumulating evidence suggests that the GM-CSF pathway may play a central role in the pathogenesis of RA, via the activation and differentiation of neutrophils and macrophages [Cornish, 2009]. GM-CSF induces the proliferation and activation of macrophage lineage cells leading to strongly increased production of key proinflammatory cytokines including TNF $\alpha$ , IL-6, and IL-1, as well as chemokines and matrix degrading proteases [Fleetwood, 2007; Gasson, 1991; Hamilton JA, 2004; Hamilton, 2013; Hart, 1991; Mantovani, 2007]. GM-CSF also serves as a differentiation factor for dendritic cells and induces upregulation of human lymphocyte antigen (HLA) class II on antigen presenting cells, which in turn will activate cluster of differentiation antigen (CD) 4+ T cells. In addition, GM-CSF is a strong chemo-attractant factor for neutrophils and induces the release of activated oxygen species from neutrophils, which can directly damage cartilage structure [Dang, 1999; Gomez-Cambronero, 2003].

GM-CSF and its receptors are found abundantly in the synovial fluid, synovial tissue and plasma of patients with RA [Bell, 1995; Davis, 2010; Fiehn, 1992]. The number of synovial CD68+ macrophages from RA patients correlates with disease activity scores, therefore, it potentially serves as a biomarker for treatment response [Bresnihan, 2009; Haringman, 2005]. The number of macrophages in synovial tissue is correlated with radiographic progression [Michelson, 1994; Mulherin, 1996]. GM-CSF also contributes to osteoclastic bone resorption which aggravates joint damage in patients with RA [Nakano, 2007]. In addition, in mouse models of collagen-induced arthritis (CIA), GM-CSF knockout or anti-GM-CSF mAb treatment reduced disease activity and prevented progression of established arthritis and, furthermore administration of recombinant GM-CSF led to exacerbation of arthritis [Campbell, 1997; Cook, 2001; Plater-Zyberk, 2007].

Taken together, pre-clinical and clinical data suggest that GM-CSF is a key mediator of inflammatory and immune disorders and may play a role in RA pathogenesis. This provides 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.

### **2.2.3. GSK3196165**

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

### **2.2.4. Clinical Data**

GSK3196165 has been studied overseas in 4 completed clinical trials, consisting of 2 studies in healthy volunteers, 1 study each in subjects with RA and multiple sclerosis (MS) (see GSK3196165 investigator's brochure [IB]).

MSC-1001 was a Phase 1b/2a multi-center, randomized, sequential group, double-blind, placebo-controlled study which evaluated the safety, preliminary efficacy, and PK of multiple doses of GSK3196165 in subjects (N=96) with active, mild-moderate RA [Behrens, 2015]. Subjects received 4 IV weekly doses of GSK3196165 at 0.3 mg/kg, 1.0 mg/kg or 1.5 mg/kg or placebo in addition to stable concomitant treatment with csDMARDs 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. Other disease activity measures (e.g., American College of Rheumatology [ACR] response) and patient-reported outcomes were consistent with the results for DAS28. GSK3196165 was generally safe and well-tolerated in this study.

Currently 3 clinical studies are on-going overseas, including 2 in RA and one in hand osteoarthritis. As for the studies in RA subjects, Study 201755 (BAROQUE) is a Phase IIb, placebo-controlled, dose-adaptive 52-week study in approximately 210 subjects with active moderate-severe RA despite treatment with MTX. Study 205180 (RENAISSANCE) is a Phase IIa, mechanistic 12-week study in approximately 40 subjects with active RA despite treatment with DMARDs.

### 3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"> <li>To assess the pharmacokinetics of GSK3196165 in Japanese RA subjects</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacokinetic parameters of GSK3196165 calculated from sparse sampling concentrations</li> </ul>
<ul style="list-style-type: none"> <li>To assess the safety and tolerability of GSK3196165 in combination with MTX therapy in Japanese RA subjects</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of adverse events, serious adverse events and adverse events of special interest</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>To assess the safety other than primary endpoints</li> </ul>	<ul style="list-style-type: none"> <li>Vital signs, 12-lead ECG and laboratory assessment</li> <li>Immunogenicity (anti-GSK3196165 antibody)</li> </ul>
<ul style="list-style-type: none"> <li>To assess the efficacy in Japanese RA subjects</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in DAS28(CRP) at all assessment timepoints</li> </ul>
<b>Exploratory</b>	
<b>Efficacy Endpoints</b>	
<p>At all efficacy assessment timepoints for</p> <ul style="list-style-type: none"> <li>ACR 20/50/70 response rate</li> <li>Change from baseline in DAS28(ESR)</li> <li>Proportion of subjects achieving categorical DAS28(CRP) / DAS28(ESR) response (moderate/good European League against Rheumatism [EULAR] response)</li> <li>Proportion of subjects achieving DAS28(CRP) / DAS28(ESR) remission</li> <li>Change from baseline in Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI)</li> <li>Change from baseline in functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue)</li> </ul> <p>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.</p>	
<b>Biomarker Endpoints</b>	
<ul style="list-style-type: none"> <li>Pharmacodynamic biomarkers to assess target engagement (e.g., serum concentration of free GM-CSF, GM-CSF-GSK3196165 complex)</li> <li>Pharmacodynamic biomarkers which may be predictive of response to GSK3196165 (e.g. 14-3-3<math>\eta</math>, MRP8/14, ARG3 neopeptide, YKL-40)</li> <li>Pharmacodynamic biomarkers to assess response to GSK3196165 (e.g. IL-6, IL-1<math>\beta</math>, TNF<math>\alpha</math>, IL-17A, IL-17F)</li> <li>Whole blood ribonucleic acid (RNA) analysis</li> </ul>	

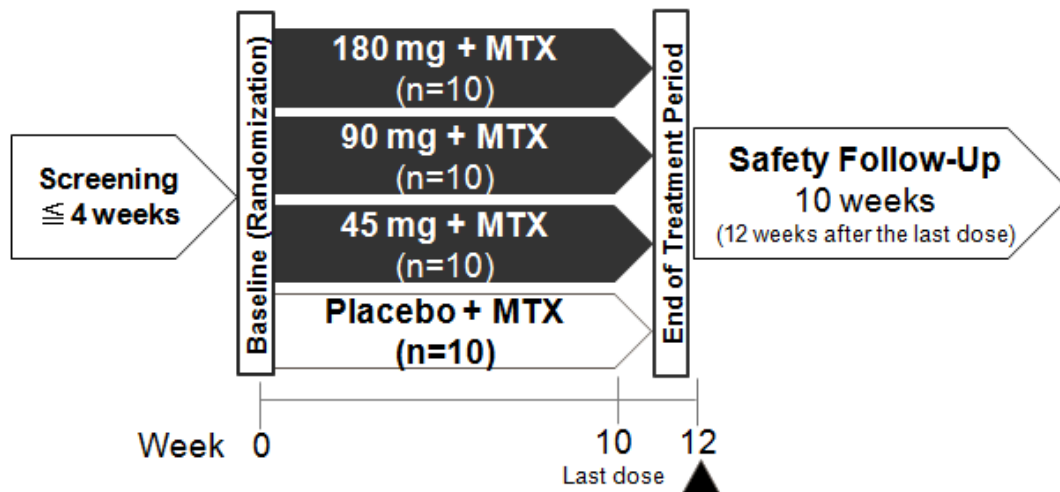
Objectives	Endpoints
<b>Safety Biomarkers</b>	
<ul style="list-style-type: none"> <li>Biomarkers which may be indicative of lung damage (e.g. surfactant D [SP-D], KL-6, cholestenic acid)</li> <li>Baseline concentrations of GM-CSF autoantibodies</li> </ul>	
<b>Other</b>	
<ul style="list-style-type: none"> <li>Pharmacogenetics (PGx): Whole blood deoxyribonucleic acid (DNA) analysis</li> </ul>	

## 4. STUDY DESIGN

### 4.1. Overall Design

- This is a randomized, double-blind, parallel group, 3 dosage level, placebo-controlled, Phase 1/2 study with the objective to assess pharmacokinetics, safety, tolerability and efficacy of GSK3196165 for 12 weeks, in combination with methotrexate (MTX), in Japanese subjects with active moderate-severe RA despite treatment with MTX.
- Approximately 40 subjects will be randomized into the study (10 subjects in each treatment groups).

**Figure 1 Study Design**



### 4.2. Treatment Arms and Duration

This study is composed of up to 4 weeks screening period, 12 weeks treatment period (last dose Week 10), and 10 weeks follow-up period (12 weeks from last dose).

Subjects will be randomized (1:1:1:1) to placebo or one of three subcutaneous (SC) GSK3196165 doses at Day 1 (Week 0).

Treatment with GSK3196165 or placebo will be given weekly as a single SC injection by an unblinded administrator. There will be 5 weekly injections (Day 1, 8, 15, 22, 29), then every other week (EOW) injections at Day 43, 57 and 71 (Week 6, 8, 10, respectively).

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

### **4.3. Type and Number of Subjects**

Target population of this study is Japanese subjects with active moderate-severe RA who previously received oral MTX (at a dose between 8-16 mg/week for at least 12 weeks, with a stable and tolerated dose for  $\geq 4$  weeks).

Approximately 55 subjects will be screened to achieve 40 randomized subjects.

### **4.4. Design Justification**

This is the first study of GSK3196165 in Japanese subjects, therefore the primary objectives of this study is to assess the pharmacokinetics, safety and tolerability of GSK3196165 in combination with MTX therapy in Japanese subjects. The overall study design is established to achieve these objectives of this study.

#### **Target population**

The target population of this study is Japanese subjects with RA. As GSK3196165 is expected to be used in combination with MTX in clinical practices, investigating PK, safety and efficacy of the drug by the combined use of MTX will be beneficial to further drug development. With reasons presented below, it is considered that this study is able to be conducted as the first study of GSK3196165 in Japanese RA subjects without previous data in healthy volunteers.

1. From the results of completed clinical studies in healthy volunteers, RA subjects, and MS subjects to date, no safety or tolerability issues have been identified with GSK3196165 (See Section 4.5 and GSK3196165 IB). There was no evidence of a dose relationship of AEs in these clinical trials.
2. One clinical study (MSC-1001) in non-Japanese subjects with RA has been completed and GSK3196165 was well tolerated in the subject population after repeat weekly administration of GSK3196165 for 4 weeks up to 1.5 mg/kg via IV route. Doses of 1.0 and 1.5 mg/kg IV weekly were associated with reduction of disease activity (see GSK3196165 IB).
3. GSK3196165 is the monoclonal antibody which binds specifically to human GM-CSF; therefore, it is not anticipated to show pharmacological effects other than the expected effect, inhibition of GM-CSF signaling.

#### **Parallel-group design**

In this study, GSK3196165 at doses of 45, 90 and 180 mg will be subcutaneously administered to Japanese subjects with RA in a parallel-group manner. The study plan is

feasible to conduct with parallel groups by implementing appropriate measures to secure the safety of study subjects in light of; i) the doses/exposures in this study remaining within a range of doses/exposures in the clinical studies conducted in the non-Japanese population, and ii) no results suggesting potential safety concerns of GSK3196165.

For potential risks of GSK3196165 administration to secure the safety of subjects (e.g., infection, pulmonary alveolar proteinosis, hypersensitive reaction, etc.), the procedures of inclusion criteria for eligible subjects, screening test, and safety monitoring during the treatment period will be set as mitigation strategies (see Section 4.6.1). Safety monitoring through multiple visits will be performed for the purpose of safety evaluation after the initial dose.

### **Placebo control**

Inclusion of a placebo arm will allow a more robust exploration of the safety profile of GSK3196165 when given in combination with MTX. The placebo arm is included also to measure the absolute effect of each dose tested.

In addition, the investigator can withdraw the subject from study at any time as clinically indicated, so subjects having insufficient benefit will not be inadequately treated.

### **Methotrexate background**

All subjects will continue to receive MTX. Although MTX dosing should be kept stable throughout the study as far as possible, dose reduction is permitted to a minimum of 8 mg/week due to intolerance or toxicity, and dose increase, following reduction, is permitted back to the subject's dose prior to reduction (maximum dose: 16 mg/week). Likewise, temporary interruption of MTX dosing for the management of intolerance will be permitted.

## **4.5. Dose Justification**

A four-fold range of doses (45-180 mg), that are expected to result in largely non-overlapping exposures, are proposed for evaluation in this study. Study agent will be administered SC weekly for 5 injections, then every other week (EOW) injections. Dosing will use fixed doses, not based on body weight (i.e. mg/kg). This reflects the change to fixed doses in the Phase IIb study (Study 201755) and the proposed future dosing of GSK3196165 in the clinical setting.

Two Phase I studies in non-Japanese healthy volunteers showed that GSK3196165 was well tolerated up to 3.0 mg/kg following single IV dose and up to 2.0 mg/kg following single SC dose. Other Phase Ib repeat dose study in subjects with MS, GSK3196165 was also well tolerated up to 2 mg/kg following the EOW administration of the investigational product for 12 weeks (see GSK3196165 IB).

In case of the lowest eligible body weight in this study (i.e. 40 kg), which would be expected to result in the highest systemic exposure, the highest planned dose of 180 mg (SC) is equivalent to 4.5 mg/kg (SC). Based on the absolute bioavailability following SC administration (~ 44%) (see GSK3196165 IB), the systemic exposure at 4.5 mg/kg (SC)



is considered to be comparable with 1.98 mg/kg (IV), which is lower than the tolerable dose in Study MSC-1000, 3.0 mg/kg (IV).

Furthermore, the maximum dose proposed, 180 mg SC has been selected to allow ample margin to the no observed adverse effect level (NOAEL), and also a margin to the no observed effect level (NOEL) (the dose at which foamy alveolar macrophages were not observed in the 26-week rhesus monkey study). A dose of 180 mg SC is predicted to result in steady-state exposures which will allow a 25-fold margin to the NOAEL (50 mg/kg), where reversible minimal to mild foamy alveolar macrophages (considered non-adverse) were seen in the 26-week monkey toxicity study, with a 3-fold margin to the NOEL (5 mg/kg) (Table 1).

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

Study/ Species	Assessment	Dose (mg/kg/wk)	AUC(0-168) <sup>a</sup> (µg.hr/mL)	AUC(0-336) <sup>b</sup> (µg.hr/mL)	Fold difference primates to human ratio	
					AUC(0-168)	AUC(0-336)
Rhesus Monkey 4 weeks IV	Week 4	5	4407	8814	2.9	NA
		25	22250	44500	14.5	
		100 <sup>c,d</sup>	55101	110201	35.9	
Cynomolgus Monkey 13week SC	Week 13	10	3149	6298	2.1	3.3
		30 <sup>d</sup>	12765	25530	8.3	13.2
		100 <sup>c</sup>	37797	75594	24.6	39.2
Rhesus Monkey 26 week IV	Week 26	5 <sup>d</sup>	2822	5644	1.8	2.9
		15	11264	22528	7.3	11.7
		50 <sup>c</sup>	24482	48963	15.9	25.4
Human 12 weeks SC <sup>e</sup>	Last dose in Induction phase (Week 4-5)		1536	-		
	Last dose in Maintenance phase (Week10-12)		-	1930		

IV intravenous; SC subcutaneous

a. AUC(0-168): As there were no significant differences on sampling occasions or gender differences within each primate study, the end of study mean values of AUC (0-168) in female and male [GSK3196165 IB: Table 10 and Table 11 in Section 4.5] have been used and divided by 2.

b. AUC(0-336): AUC (0-168) have been multiplied by 2 to obtain mean concentrations over a two week period.

c. No observed adverse effect dose level (NOAEL).

d. No observed effect dose level (NOEL).

e. Simulated median AUC based on analysis of SC data from study MOR103C104 with a 2 compartment PK model.

The dose range includes doses that are anticipated to be effective or minimally effective based on the results as follows:

- In the Phase 1b/2a RA study (Study MSC-1001), IV doses of 1.0 mg/kg and 1.5 mg/kg showed activity and 0.3 mg/kg showed little to no activity after 4 weeks of weekly treatment (see GSK3196165 IB).
- Complete inhibition of GM-CSF function by GSK3196165 has been observed in different assays in vitro at mean concentrations averaging 0.2 µg/mL. Although the level of penetration of GSK3196165 into the inflamed synovial tissues is not known, it is reasonable to assume that its penetration rate is in the range as seen with other mAbs. Concentration levels of mAbs in the synovium vary among patients and have been reported to be below 30% of the plasma values [Choy, 2000]. Based on a 30% penetration rate, the continuous GM-CSF production and considering patient heterogeneity, the minimal or sub-optimal clinical effect level is anticipated to be at approximately 10-fold higher (2 µg/mL) than the inhibitory concentration derived from in vitro studies.

Doses of 90 and 180 mg SC given EOW are anticipated to result in steady state C<sub>min</sub> concentration levels of approximately 2 µg/mL or greater (a hypothetical target to bind synovial GM-CSF, see GSK3196165 IB). The weekly loading dose regimen is intended to achieve rapid reduction in disease activity, as supported by the completed 4-week RA study (Study MSC-1001) where doses of 1.0 and 1.5 mg/kg IV weekly were associated with reduction of DAS28 score after the first dose that continued to decrease through Week 10 and 6, respectively (see GSK3196165 IB).

Therefore, the dose range in this study (45, 90 and 180 mg [SC]) is considered to be safe and appropriate. Also, using this range will allow us to assess linearity in pharmacokinetics of GSK3196165 in Japanese subjects.

#### **4.6. Benefit:Risk Assessment**

Summaries of findings from both non-clinical and clinical studies conducted with GSK3196165 can be found in the GSK3196165 IB. 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
<p><b>Infections</b></p>	<p>Immune-modulating biologic drugs used in RA (such as anti-TNF agents) are associated with an increased risk of serious and opportunistic infections. Similarly, because of the role of GM-CSF in anti-infective immunity, GSK3196165 also has the potential to increase the risk of infection.</p> <p><b>Non-clinical Data:</b></p> <p>No changes in peripheral blood populations (lymphocytes, neutrophils, monocytes, eosinophils or basophils), phagocytic activity of peripheral blood polymorphonuclear cells (26-week study in rhesus monkey), T-cell dependent B-cell primary or secondary response, or circulating cytokine levels (26-week study in rhesus monkey) were observed.</p> <p>Studies in knock-out mice showed that GM-CSF deficiency (GM-CSF<sup>-/-</sup>) affects the ability of mice to control infection when infected with M. tuberculosis or pulmonary group B streptococcus [LeVine, 1999].</p> <p><b>Clinical Data:</b></p> <p>One healthy volunteer in study MSC-1000 experienced septic shock secondary to pneumonia 29 days after receiving a single dose of IP at 1.5 mg/kg. Subject recovered after treatment with antibiotics, and the subject completed the study follow-up period as per protocol.</p> <p>One RA subject in study MSC-1001 experienced serious pleurisy which responded to antibiotics.</p>	<p><b><u>Subject selection (see Section 5.2):</u></b></p> <ul style="list-style-type: none"> <li>• Subjects with active infections, or a history of recent infections (hospitalization within the last six months) or recurrent infections are not permitted to enter the study.</li> <li>• Subjects with significant leukopenia are not permitted to enter the study.</li> <li>• Subjects will be screened for significant neutropenia, TB, HIV and Hepatitis B and C, and excluded from study participation if positive.</li> <li>• Subjects with a recent vaccination (live or attenuated) or a planned live vaccination are not permitted to enter the study.</li> </ul> <p><b><u>Subject monitoring:</u></b></p> <ul style="list-style-type: none"> <li>• Serious infections and opportunistic infections are categorised as adverse events of special interest (AESIs).</li> <li>• Subjects will be monitored for infection according to standard of care for subjects receiving any immune-modulating biologic therapy for RA. Appropriate diagnostic tests will be considered during the study if clinically indicated to secure the safety of subjects.</li> <li>• Subjects will be instructed as to the signs and symptoms of infection, and to contact site personnel should they develop. This information will also be contained within the patient Informed Consent Form.</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		<ul style="list-style-type: none"> <li>When subjects are considered to be at high risk of pneumocystis pneumonia (PCP) after the initiation of treatment by the investigator's judgement, preventive dosing of co-trimoxazole is permitted.</li> </ul> <p><b><u>Withdrawal criteria:</u></b></p> <ul style="list-style-type: none"> <li>In the event of a serious or opportunistic infection, study medication should be discontinued and the subject withdrawn from the study.</li> </ul>
<p><b>Pulmonary alveolar proteinosis (PAP)</b></p>	<p>GM-CSF signalling is required to maintain the normal function of alveolar macrophages. Long-term absence of GM-CSF signalling (e.g., via hereditary GM-CSF deficiency or development of anti-GM-CSF auto-antibodies) is known to cause the extremely rare condition of PAP, which is characterized by the accumulation of surfactant lipids and protein in the alveolar spaces, with resultant impairment in gas exchange.</p> <p><b>Non-clinical Data:</b></p> <p>Non-adverse minimal to mild foamy alveolar macrophage accumulation were noted in lungs of monkeys in the 13-week SC and 26-week IV toxicology studies, but reversible following off drug period. Dose levels at which foamy alveolar macrophages were not observed were identified in these studies.</p> <p><b>Clinical Data:</b></p> <p>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</p>	<p><b><u>Subject selection (see Section 5.1 and Section 5.2):</u></b></p> <ul style="list-style-type: none"> <li>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.</li> <li>Pulmonary function testing (spirometry, Diffusing capacity of the lung for carbon monoxide [D<sub>LCO</sub>] measurements) will be performed at screening in order to exclude those subjects with moderate-severe impairment.</li> </ul> <p><b><u>Dose Duration:</u></b></p> <ul style="list-style-type: none"> <li>The exposure duration to GSK3196165 in this study is 12 weeks. Although the time course of PAP development in humans is unknown, the published literature suggests that it requires full inhibition of GM-CSF for years before clinical manifestation of the disease can be detected (refer to GSK3196165 IB for further details). Therefore, the risk of development of PAP in this study</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	pulmonary functions.	<p>is anticipated to be low.</p> <p><b><u>Subject Monitoring:</u></b></p> <ul style="list-style-type: none"> <li>• Specific pulmonary assessments are a requirement of the study protocol: <ul style="list-style-type: none"> <li>• Subjects will be assessed every visit for the development of cough and dyspnea, and will also have regular chest auscultation and pulse oximetry measurements. PAP, persistent cough or dyspnea will be categorised as AESIs.</li> <li>• Pulmonary function testing (spirometry and D<sub>LCO</sub> measurements) will be performed at screening, Week 12 and at the follow-up visit. Relative change in D<sub>LCO</sub> &gt;15% from screening or non life threatening pulmonary changes related to surfactant accumulation will be categorised as AESIs if confirmed with three consecutive weekly tests.</li> </ul> </li> <li>• In the event of clinically-significant pulmonary events, the subject should be referred to a pulmonologist for further assessment. The study drug should be suspended until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined and clinically significant events have been excluded by the pulmonologist. Suggested pulmonary assessment and management algorithms will be provided in the Study Reference Manual (SRM).</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		<p><b><u>Withdrawal criteria:</u></b></p> <ul style="list-style-type: none"> <li>In the event of a confirmed PAP, study medication should be discontinued and the subject withdrawn from the study.</li> </ul>
<p><b>Hypersensitivity reactions, including anaphylaxis</b></p>	<p>There is a potential risk of hypersensitivity reactions, including anaphylaxis, during and following the administration of protein-based products, such as GSK3196165.</p> <p><b>Clinical Data:</b></p> <p>No allergic or acute systemic reactions have been observed to date in the clinical development program.</p>	<p><b><u>Subject selection (see Section 5.2):</u></b></p> <ul style="list-style-type: none"> <li>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.</li> </ul> <p><b><u>Study treatment administration/Subject monitoring:</u></b></p> <ul style="list-style-type: none"> <li>All SC administrations will be performed at the clinical site.</li> <li>Subjects will be required to remain monitored at the site for 1 hour after the injection for the first 3 injections, and then for 30 minutes for subsequent injections.</li> <li>Subjects should be informed of the signs and symptoms of an acute hypersensitivity reaction, and be instructed to seek immediate medical care should they develop. This information will also be contained within the patient Informed Consent Form.</li> <li>Should hypersensitivity or anaphylaxis occur, subjects should be managed appropriately per local guidelines/medical judgement.</li> <li>Hypersensitivity reactions, including anaphylaxis are categorised as AESIs.</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		<p><b><u>Withdrawal criteria:</u></b></p> <ul style="list-style-type: none"> <li>In the event of severe or serious hypersensitivity reactions including anaphylaxis, study medication should be discontinued and the subject withdrawn from the study.</li> </ul>
<p><b>Injection site reactions</b></p>	<p>SC injections may be associated with local reactions (e.g., swelling, induration, pain).</p> <p><b>Non-clinical &amp; Clinical Data:</b></p> <p>No macroscopic or microscopic changes indicative of local injection site reactions were observed following IV or SC administration.</p>	<p><b><u>Subject monitoring:</u></b></p> <ul style="list-style-type: none"> <li>Subjects should be monitored for injection site reactions throughout the study, and the information recorded in the eCRF.</li> <li>Injection sites will be rotated.</li> <li>Injection site reactions are categorised as AESIs.</li> </ul>
<p><b>Leukopenia</b></p>	<p>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].</p> <p><b>Non-clinical &amp; Clinical Data:</b></p> <p>There have been no reports of neutropenia or decreases in leukocytes in the non-clinical and clinical GSK3196165 program.</p>	<p><b><u>Subject selection (see Section 5.2):</u></b></p> <ul style="list-style-type: none"> <li>Subjects with significant leukopenia (<math>\leq 3.0 \times 10^9/L</math>); thrombocytopenia (platelet count <math>\leq 100 \times 10^9/L</math>); neutropenia (absolute neutrophil count <math>\leq 1.5 \times 10^9/L</math>); lymphocytopenia (<math>\leq 0.5 \times 10^9/L</math>) within 4 weeks prior to Day 1 are not permitted to enter the study.</li> </ul> <p><b><u>Subject monitoring:</u></b></p> <ul style="list-style-type: none"> <li>A full blood count (with differential) will be performed at regular intervals throughout the study (ref. Time and Events Table, Section 7.1).</li> <li>Grade 3 or greater neutropenia is categorised as an AESI.</li> </ul> <p><b><u>Withdrawal criteria:</u></b></p> <ul style="list-style-type: none"> <li>In the events of significant leukopenia (<math>&lt; 2.0 \times 10^9/L</math>); neutropenia (absolute neutrophil count <math>&lt; 1.0 \times 10^9/L</math>); lymphocytopenia (<math>&lt; 0.5 \times 10^9/L</math>), study medication should be</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		discontinued and the subject withdrawn from the study.
<b>Reproductive toxicity</b>	<p>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.</p> <p><b>Non-clinical data</b></p> <p>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.</p> <p>The effect on human pregnancy is unknown.</p> <p><b>Clinical Data:</b></p> <p>No HVs or RA subjects became pregnant during the studies, but one MS subject was found to be pregnant during study MOR103C103 and received four 2.0 mg/kg doses, the pregnancy was terminated 2 weeks later by elective abortion.</p>	<p><b><u>Subject selection (see Section 5.1):</u></b></p> <ul style="list-style-type: none"> <li>Male and female subjects will only be permitted to enter the study if they meet the contraception requirements detailed in inclusion criterion #10 and <a href="#">Appendix 2</a>.</li> </ul> <p><b><u>Subject monitoring:</u></b></p> <ul style="list-style-type: none"> <li>Females of child bearing potential will undergo pregnancy testing at screening and at regular intervals during the study (ref. Time and Events Table, Section 7.1).</li> </ul> <p><b><u>Withdrawal criteria:</u></b></p> <ul style="list-style-type: none"> <li>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.</li> </ul> <p><b><u>Other considerations:</u></b></p> <ul style="list-style-type: none"> <li>Subject will be followed to determine the outcome of the pregnancy</li> <li>Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.</li> </ul>
<b>Malignancy</b>	<p>The risk of malignancy is increased in patients with RA. In addition, immunomodulatory therapies may increase the risk of malignancy.</p> <p><b>Non-clinical &amp; Clinical Data:</b></p> <p>There have been no reports of malignancy in the non-clinical and clinical GSK3196165 program.</p>	<p><b><u>Subject selection (see Section 5.2):</u></b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>



#### **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 (Study MSC-1001) in subjects with active RA [Behrens, 2015]. In addition, mavrilimumab (an anti-GM-CSF  $\alpha$ -subunit receptor mAb), has also shown substantial activity in RA subjects who had an inadequate response to MTX in studies of up to 24 weeks of dosing [Burmester, 2013; Burmester, 2014]. These data support the clinical evaluation of GSK3196165 in subjects with RA.

#### **4.6.3. 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.

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). Appropriate safety monitoring will be undertaken in studies of GSK3196165 to proactively address and mitigate the potential risks. Recent data with mavrilimumab administered for 24 weeks in combination with MTX in subjects with active RA [Burmester, 2014] provides further support that targeting this pathway is associated with an acceptable benefit:risk profile.

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

### **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.

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:

<b>AGE</b>
1. Age $\geq 20$ years at the time of signing informed consent.
<b>TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY</b>
2. Japanese RA subjects who meets ACR/EULAR 2010 RA Classification Criteria.
3. Functional class I, II or III defined by the 1992 ACR Classification of Functional Status in RA.
4. Disease duration of $\geq 12$ weeks (time from onset of patient-reported symptoms of either pain or stiffness or swelling in hands, feet or wrists).
5. Swollen joint count of $\geq 4$ (66-joint count) and tender joint count of $\geq 4$ (68-joint count) at screening and at Day 1.
6. DAS28(CRP) $\geq 3.2$ at screening.
7. C-Reactive Protein (CRP) $\geq 0.3$ mg/dL at screening.
8. Must have previously received MTX (8-16 mg weekly) orally for at least 12 weeks before screening, with a stable and tolerated dose for $\geq 4$ weeks prior to Day 1.
<b>WEIGHT</b>
9. Weight $\geq 40$ kg.
<b>SEX</b>
10. Male or female subjects are eligible to participate so long as they meet and agree to abide by the contraceptive criteria detailed in <a href="#">Appendix 2</a> .
<b>INFORMED CONSENT</b>
11. Written informed consent prior to any of the screening procedures including discontinuation of prohibited medications.

## OTHER SAFETY-RELATED

12. Willing to continue or initiate treatment with oral folic acid (5 mg/week) and be treated during the entire study (mandatory co-medication for MTX treatment).
13.  $D_{LCO} \geq 60\%$ <sup>1)</sup> predicted; forced expiratory volume in 1 second ( $FEV_1$ )  $\geq 70\%$  predicted; forced vital capacity (FVC)  $\geq 80\%$  predicted.
- 1) For subjects with  $D_{LCO}$  values  $\geq 60\%$  to  $< 70\%$ , 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.
14. No evidence of active or latent infection with *Mycobacterium tuberculosis* (TB), as defined by all of the following:
- 1) No history of active or latent TB infection irrespective of treatment status.
  - 2) A negative T-spot test within 4 weeks of baseline (Day 1).
  - 3) Chest X-ray within 12 weeks of Day 1, locally read by a radiologist, with no evidence of current or previous pulmonary tuberculosis.  
NB: If there is suspicious of risk for TB infection because of 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 women.
2. History of other inflammatory rheumatological or autoimmune disorders, other than Sjögren's syndrome secondary to RA.
3. History of any respiratory disease which (in the opinion of the investigator) would compromise subject safety or the ability of the subject to complete the study (e.g. significant interstitial lung disease, such as pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), moderate-severe asthma, bronchiectasis, previous PAP).
4. Clinically-significant or unstable (in the opinion of the investigator) persistent cough or dyspnea that is unexplained.
5. QT interval corrected for heart rate (QTc)  $> 450$ msec 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)  $\geq 1.5x$  upper limit of normal (ULN); aspartate transaminase (AST)  $\geq 1.5x$ ULN; alkaline phosphatase and bilirubin  $\geq 1.5x$ ULN (isolated bilirubin  $> 1.5x$ ULN 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. Clinically significant unstable or uncontrolled acute or chronic disease (e.g., cardiovascular including uncompensated congestive cardiac failure New York Heart Association [NYHA] III or IV, myocardial infarction within 12 months, unstable angina pectoris, uncontrolled hypertension, uncontrolled hypercholesterolemia) pulmonary, hematologic, gastrointestinal (including Crohn's Disease or ulcerative colitis), hepatic, renal, neurological, psychiatric, malignancy, endocrinological or infectious diseases, which, in the opinion of the investigator, could confound the results of the study or put the subject at undue risk.
9. A history of malignant neoplasm within the last 10 years or breast cancer within the last 20 years, except for non-melanoma skin cancers that have been excised and cured or carcinoma in situ of the uterine cervix.
10. Kidney disease: Current or history of renal disease, or estimated creatinine clearance  $< 60$  mL/min/1.73 m<sup>2</sup> (MDRD formula) or serum creatinine  $> 1.5x$ ULN within 4 weeks of Day 1.
11. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
12. History of infected joint prosthesis at any time, with the prosthesis still in situ. History of leg ulcers, catheters, chronic sinusitis or recurrent chest or urinary tract infections.
13. Active infections, or history of recurrent infections (excluding recurrent fungal infections of the nail bed), or have required management of acute or chronic infections, as follows:
  - i) Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).  
OR
  - ii) Hospitalization for treatment of infection within 26 weeks of Day 1.  
OR
  - iii) Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 26 weeks of Day 1 or oral

antimicrobials within 2 weeks of Day 1.

14. A vaccination (live or attenuated) within 30 days of Day 1 or Bacillus Calmette-Guérin (BCG) vaccination within 1 year of Day 1, or a live vaccination planned during the course of the study (including follow-up period).
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 (including follow-up period).

#### CONCOMITANT MEDICATIONS

16. Use of prohibited medications Prior to AND throughout the study:

- Any conventional DMARDs other than MTX (including sulfasalazine, bucillamine, iguratimod, tacrolimus) should be withdrawn at least 2 weeks prior to Day 1.
  - Subjects may require longer to discontinue azathioprine or leflunomide prior to Day 1:
    - i) Azathioprine must be discontinued  $\geq 4$  weeks prior to randomization.
    - ii) Leflunomide must be discontinued  $\geq 12$  weeks prior to Day 1 (or  $\geq 14$  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 4 weeks prior to Day 1.
- Any biologic agents (such as TNF inhibitors [including adalimumab, etanercept, infliximab, certolizumab pegol, golimumab] or non-TNF inhibitors [including abatacept, rituximab, tocilizumab, belimumab]).
- Any Janus kinase (JAK) inhibitors (such as tofacitinib).
- Any anti-rheumatic investigational compounds.
- Any alkylating agents (such as cyclophosphamide).
- Plasmapheresis or intravenous immunoglobulin (IVIG) within 26 weeks of Day 1.

17. Corticosteroids:

- Any IM, IV or IA corticosteroids within 8 weeks of Day 1.
- Oral corticosteroids:
  - Any treatment with  $>10$  mg/day dose oral prednisolone (or equivalent) within 4 weeks of Day 1.
  - New oral corticosteroid or changes in corticosteroid dose within the 4 weeks prior to Day 1. (New topical steroids and immunosuppressive agents (e.g., eye drops, creams) are permitted).

## 18. Non-steroidal anti-inflammatory drugs (NSAIDs):

- New or change in dose of NSAID within 2 weeks of Day 1.

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

## RELEVANT HABITS

20. 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

21. 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

22. Abnormal chest X-ray within 12 weeks of Day 1 (locally read and reported by a radiologist) judged by the investigator as clinically-significant.

23. Any Grade 3 or 4 hematology or clinical chemistry laboratory abnormality [CTCAE, 2009 v4.0] within 4 weeks of Day 1.

24. Hemoglobin  $\leq 9$  g/dL; white blood cell count  $\leq 3.0 \times 10^9/L$ ; platelet count  $\leq 100 \times 10^9/L$ ; absolute neutrophil count  $\leq 1.5 \times 10^9/L$ ; lymphocyte count  $\leq 0.5 \times 10^9/L$  within 4 weeks of Day 1.

25. Serologic evidence of current/previous Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg) and anti-Hepatitis B core (anti-HBc) antibody as follows within 4 weeks of Day 1.

- Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
- Subjects with positive anti-HBs antibody and HBV-DNA ( $\geq 2.1$  log copies/mL) are excluded.

26. Hepatitis C: Positive test for Hepatitis C virus (HCV) antibody confirmed on a subsequent blood sample by RNA-PCR assay within 4 weeks of Day 1.

- Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.

27. Positive serology for human immunodeficiency virus (HIV) 1 or 2 (within 4 weeks of Day 1).

### **5.3. Screening/Baseline Failures**

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

#### **5.3.1. Re-Screening**

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

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

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

#### **5.3.2. Re-Testing**

##### **5.3.2.1. Laboratory tests**

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

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

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

##### **5.3.2.2. Pulmonary Function Tests**

It is permitted to repeat the pulmonary function testing sessions (spirometry and/or  $D_{LCO}$ ) once within the screening period. If the screening  $D_{LCO}$  result is  $\geq 60\%$  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. ECG test

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

## 5.4. Withdrawal/Stopping Criteria

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

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

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

- All serious or opportunistic infections.
- Pregnancy.
- Confirmed PAP.
- Severe or serious hypersensitivity reactions, including anaphylaxis.
- If the liver chemistry stopping criteria (Section 5.4.1) or QTc stopping criteria (Section 5.4.2) are met.
- Persistent or recurrent hematological laboratory abnormalities (see Section 5.5.2).
- Detected ( $\geq 2.1$  log copies/mL) HBV DNA for subjects who have positive anti-HBs antibody.
- Other serious or severe adverse events, at the discretion of the investigator, after consultation with the Medical Monitor.



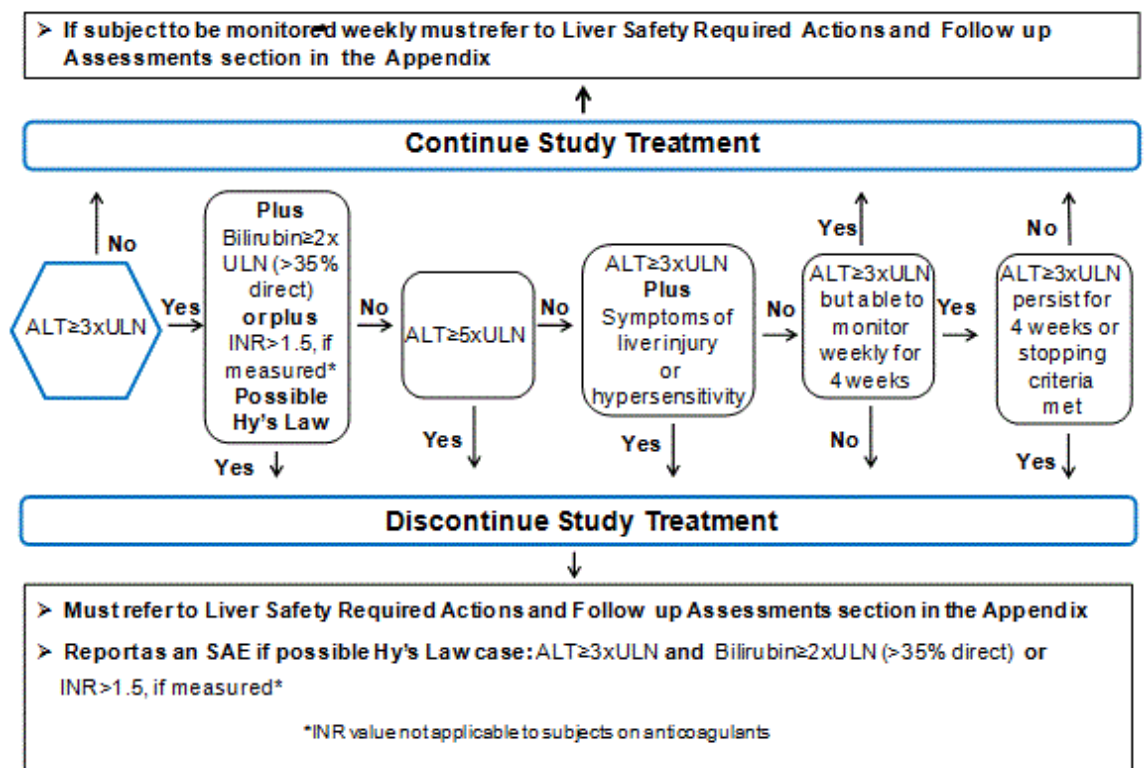
If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Any subject who withdraws must complete an early withdrawal visit, and the 10-week follow-up visit (from withdrawal visit).

#### 5.4.1. Liver Chemistry Stopping Criteria

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

##### 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 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 QT interval corrected for heart rate according to Fridericia's formula (QTcF) *must* be used to determine eligibility for and discontinuation from the study.

- The QTcF 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 single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period.

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

- QTc >500 msec OR uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

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) for three consecutive weeks.
- Persistent dyspnea (Borg scale grade 3 or above) for three consecutive weeks.

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. 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 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<sup>9</sup>/L

- Absolute neutrophil count <  $1.0 \times 10^9/L$
- Lymphocyte count <  $0.5 \times 10^9/L$

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  $\geq 2$  sequential tests), or occur recurrently (on 2 separate occasions), study medications will be permanently discontinued and the subject withdrawn from the study.

## 5.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit. The end of the study is defined as the last subject's last visit.

## 6. STUDY TREATMENT

### 6.1. Investigational Product and Other Study Treatment

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

**Table 2 Investigational Product and Other Study Treatment**

	Investigational Product		Co-medication
	Test	Control	
<b>Product name:</b>	GSK3196165	Placebo	Methotrexate and folic acid.
<b>Physical description:</b>	Sterile, aqueous solution of purified monoclonal antibody 150 mg/mL	Sterile 0.9% (weight/volume [w/v]) sodium chloride solution	-
<b>Dosage form:</b>	Liquid (Subcutaneous injection preparation in a glass vial containing 1.2 mL of GSK3196165)	Liquid (Injection preparation in plastic ampoule containing 20 mL saline)	MTX: tablet, capsule Folic acid: tablet
<b>Route of Administration:</b>	SC injection	SC injection	Oral

	Investigational Product		Co-medication
	Test	Control	
<b>Dosage levels (volumes):</b>	45 mg (0.3 mL) 90 mg (0.6 mL) 180 mg (1.2 mL)	- (0.6 mL)	MTX:8-16 mg/week Folic acid: 5 mg/week. Note: Folic acid dose may be increased to counteract side-effects of MTX (including nausea, mucositis, and headache).
<b>Dosing instructions:</b>	<p>Investigator product (GSK3196165 or placebo) will be administered SC weekly for 5 injections, and then EOW injections. Investigational product should be administered SC into thigh or abdomen. Sites should be rotated, and it should be administered in different site than previous one.</p> <p>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.</p> <p>Subjects will be randomized as shown in Time and Events Table, Section 7.1, and the dosing schedule should be followed as closely as possible. GSK3196165/placebo should be administered on the same day each week <math>\pm</math> 1 day for the first 5 weekly doses (with a minimum of 5 days between doses, for no more than 2 consecutive doses). Following this GSK3196165/placebo should be administered on the same day EOW <math>\pm</math> 3 days (with a minimum of 8 days between doses).</p> <p>GSK3196165/placebo will be discontinued or interrupted as described in Section 5.4 or Section 5.5.</p>		<p>MTX and folic acid should be started prior to and maintained during the study.</p> <p>MTX: can be taken as a single weekly dose, or divided weekly dose, per investigator's discretion.</p> <p>Folic acid: should be taken within 24-48 hours following MTX administration.</p>

	Investigational Product		Co-medication
	Test	Control	
<b>Storage Condition</b>	GSK3196165 should be stored under cold chain condition (2-8°C, protected from light).	Placebo should be stored at room temperature and protected from excessive heat and freezing.	-
<b>Manufacturer/ Source of procurement</b>	GSK	Otsuka Pharmaceutical Factory, Inc..  (Provided by GSK)	-

Further details of study treatment information are provided in the SRM.

### Co-administration drug

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

#### 1. MTX

Subjects will receive 8-16 mg/week MTX orally. MTX dosing should be kept stable throughout the study as far as possible. Dose reduction is permitted to a minimum of 8 mg/week due to intolerance or toxicity, and dose increase, following reduction, is permitted back to the subject's dose prior to reduction (maximum dose 16 mg/week). Likewise, temporary interruption of MTX dosing for the management of intolerance will be permitted.

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

#### 2. Folic acid

Subjects will receive 5 mg/week folic acid orally. The dosing regimen is at the discretion of the investigator. Folic acid should be taken within 24-48 hours following the MTX. Folic acid dose may be increased to counteract side-effects of MTX (including nausea, mucositis, and headache).

## 6.2. Treatment Assignment

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

The study will use central randomization and the randomization schedule will be generated by Clinical Statistics using validated randomization software.

Randomization numbers will be assigned to subjects by patient registration center.

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.

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

Further details of treatment assignment are provided in the SRM.

### **6.3. Planned Dose Adjustments**

This protocol does NOT allow dose adjustments of investigational product.

### **6.4. Blinding**

The study will be double-blind, which means that the investigator and trial staff at site (apart from the unblinded administrator), subject, and sponsor personnel (apart from the unblinded monitor and the unblinded data manager) will be blinded to the trial treatment allocated to each individual subject.

There will be at least one unblinded administrator that will prepare and administer the study treatment and will not perform any other study procedures. A shield (e.g., eye mask) will be used during investigational product administration so that subjects are not able to see the injection volume, syringe size, or any difference in color between GSK3196165 and placebo.

#### **Emergency Key Code Unblinding**

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

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

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

### **6.5. Packaging and Labeling**

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

### **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 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 unblinded administrator designated by investigator.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS) 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.

### **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. 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 and folic acid. The date taken and total weekly dose will be recorded in the eCRF.

## **6.8. Treatment of Study Treatment Overdose**

### **6.8.1. Overdose of GSK3196165**

For this study, any dose of GSK3196165 > 180 mg within one week time period will be considered an overdose. There is very limited clinical safety data at this stage of development. However there have been no reports of overdose with GSK3196165 to date. The risk of overdose occurring is considered low because in GSK3196165 will be administered by an independent administrator (an unblinded site staff), and the maximum volume that can be withdrawn from the vial is equivalent to the highest dose (of 180 mg) to be evaluated. No specific treatment is recommended for an overdose of GSK3196165, and the investigator should treat as clinically indicated. Details (amount of investigational product given and any resulting AEs/SAEs) should be recorded in the eCRF.

In the event of an overdose the investigator should:

1. contact the Medical Monitor immediately.
2. closely monitor the subject for AEs/SAEs and laboratory abnormalities.
3. obtain a plasma sample for PK analysis at the time of the event, and three days after the event (unless otherwise requested by the Medical Monitor).
4. 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**

#### **Signs and symptoms:**

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following overdose include hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

#### **Treatment:**

In case of overdosage, leucovorin administration, which diminishes the toxicity and counteracts the effect of MTX, should begin as promptly as possible together with hydration and urinary alkalinization to promote elimination of MTX. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity may decrease.



## 6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and other treatment options are available.

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 metabolising enzymes has become increasingly evident [Lee, 2010; Zhou, 2011; Evers, 2013]. During inflammation, enzymes such as Cytochrome P (CYP) 450 can be down-regulated leading to instances of reduced clearance and increased plasma concentrations of administered drugs.

The administration of GSK3196165 can potentially alter circulating cytokine levels to a patient whose cytokine levels have been elevated. This may partially or completely reverse the impact of cytokines on CYP450 enzymes leading to changes in the exposure of co-administered drugs whose metabolism is dependent on CYP450 enzymes. The reports so far suggest the magnitude of drug interaction by therapeutic proteins (clinically) is generally small (less than two-fold) and therefore only likely to be clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of GSK3196165, in subjects being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g. theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when GSK3196165 is co-administered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of GSK3196165 on CYP450 enzyme activity may persist for several weeks after stopping therapy.

### 6.10.1. Permitted Medications and Non-Drug Therapies

All permitted medications, and non-drug therapies that may affect RA disease activity or assessments will be recorded in eCRF.

#### 6.10.1.1. Oral Corticosteroids

Stable use of oral corticosteroids  $\leq 10$  mg/day prednisone or equivalent agent is permitted if the dose is stable for at least 4 weeks prior to Day 1 (baseline). This dose should remain constant throughout the first 12 weeks of the study. Dose changes before Week 12 are not permitted, unless required for safety or tolerability.

**6.10.1.2. NSAID**

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

**6.10.1.3. Analgesics**

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

**6.10.1.4. Chinese traditional medicine**

Stable use of Chinese traditional medicine that has indications for RA is permitted if the dose is stable for at least 4 weeks prior to Day 1 (baseline). This dose should remain constant throughout the first 12 weeks of the study.

**6.10.2. Prohibited Medications and Non-Drug Therapies****6.10.2.1. Related to the Study**

- Any conventional DMARDs other than MTX (including leflunomide, sulfasalazine, azathioprine, bucillamine, iguratimod, tacrolimus).
- Any biologic agent (such as TNF inhibitors such as adalimumab, etanercept, infliximab, certolizumab pegol, golimumab or non-TNF inhibitors (including abatacept, rituximab, tocilizumab and belimumab), tofacitinib and any anti-rheumatic investigational compounds).
- Any alkylating agents (such as cyclophosphamide).
- Plasmapheresis or intravenous immunoglobulin (IVIG).
- Oral corticosteroid above 10 mg/day prednisone or equivalent agent.
- 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 4 weeks prior to Day 1, or throughout the study.
- Live vaccines should not be administered for at least 30 days (or 1 year for BCG vaccination) prior to Day 1, or 12 weeks after the last dose of GSK3196165. On the other hand, inactivated vaccines (including toxoid) can be administered throughout the study. However, 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 law and guideline.

#### **6.10.2.2. Related to Methotrexate**

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

- Prohibited:
  - Concomitant administration of folate antagonists such as co-trimoxazole\* (trimethoprim-sulfamethoxazole), triamterene and nitrous oxide are prohibited.  
\*: When a preventive dose is required for subjects considered at high risk of pneumocystis pneumonia (PCP) after the initiation of treatment by the investigator's judgement, the approved low dose of co-trimoxazole is allowed (1 tablet daily or 3 times a week).
  - Vitamin preparations containing folic acid or its derivatives may alter response to MTX (although folic acid is required to reduce the side-effects of MTX, it must not be administered on the same day as MTX).
- Caution:
  - The following medications may increase side-effects of MTX (including bone-marrow suppression, hepatotoxicity, nephrotoxicity, gastrointestinal toxicity).
    - NSAIDs (including salicylates)
    - sulfonamides, tetracyclines, chloramphenicol, phenytoin, barbituric acid derivatives
    - penicillins (including piperacillin sodium), probenecid
    - ciprofloxacin
  - The following medication may photosensitivity.
    - porfimer sodium

#### **6.10.2.3. Complementary Therapies other than Chinese traditional medicine**

The use of complementary therapies that may affect RA disease activity or assessments, including, but not limited to, traditional medicine (e.g. Acupuncture, Ayurveda) 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).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order before administration of study treatment:
  - 1) Patient- reported outcome (PRO) assessments
  - 2) 12-lead ECG
  - 3) vital signs
  - 4) blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

7.1. Time and Events Table

Procedures	Screening	Baseline		Treatment Period										FU		Last Visit	EW <sup>1</sup>
	Visit																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
	Week (up to 4 weeks)	0	1	2	3	4	6	8	10	12	15	18	22				
Day																	
	1	3*	8	15	22	29	43	57	71	74*	85	106	127	155			
Allowance		±1 day					±3 days				±1 day	±3 days	±1 week				
Written Informed Consent(s)	X																
Subject Demography	X																
Medical, Disease, Therapy History	X																
Inclusion/Exclusion Criteria	X																
Efficacy and PRO Assessments <sup>3</sup>																	
Swollen (66) & Tender (68) Joint Count <sup>2</sup>	X	X <sup>4</sup>		X	X		X	X	X			X			X	X	
Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis <sup>3</sup>	X	X <sup>4</sup>		X	X		X	X	X			X			X	X	
HAQ-DI <sup>3</sup>	X	X <sup>4</sup>		X	X		X	X	X			X			X	X	
FACIT-Fatigue <sup>3</sup>		X <sup>4</sup>					X					X			X	X	
Safety Evaluations <sup>5</sup>																	
Concomitant Medication	X	X	Record all concomitant medications														
Height <sup>6</sup> , Body weight	X						X					X			X	X	
Other Physical Examination <sup>7</sup>	X	X <sup>4</sup>		X	X		X		X		X			X	X	X	
Vital Signs	X	X		X	X	X	X	X	X	X		X			X	X	
12-lead ECG <sup>8</sup>	X											X				X	
AEs/SAEs/AESIs	X <sup>9</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cough, Lung Auscultation, Pulse Oximetry, Borg Dyspnea Scale	X	X <sup>4</sup>		X	X	X	X	X	X	X		X			X	X	
Chest X-ray <sup>10</sup>	X																
Spirometry (FEV <sub>1</sub> , FVC)	X											X			X	X	
DLCO	X <sup>11</sup>											X			X	X	

Procedures	Screening	Baseline		Treatment Period								FU		Last Visit	EW <sup>1</sup>	
	Visit															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	Week (up to 4 weeks)	0	1	2	3	4	6	8	10	12	15	18	22			
	Day	1	3*	8	15	22	29	43	57	71	74*	85	106	127	155	
Allowance		±1 day			±3 days			±1 day		±3 days		±1 week				
Laboratory Assessments																
Hematology, Chemistry (except for lipid and pregnancy test)	X	X <sup>4</sup>		X		X		X		X		X		X	X	
Urinalysis (dip stick)	X					X		X		X		X		X	X	
Cholesterol, triglycerides, HDL, LDL <sup>12</sup>		X <sup>4</sup>								X		X		X	X	
Pregnancy test <sup>13</sup>	S	U				U		U		U		U		U	U	
TB, HBsAg, HepB cAb, HBs Ab, HepC Ab, HIV, HBV DNA**	X															
HBV DNA monitoring (HBs Ab positive subject only)						X		X		X		X	X	X	X	
RF, ACPA (anti-CCP)	X															
ESR <sup>14</sup>		X <sup>4</sup>		X	X		X	X	X		X			X	X	
CRP	X	X <sup>4</sup>		X	X		X	X	X		X			X	X	
Other Laboratory Assessments																
PK blood sampling (GSK3196165) <sup>15</sup>		X <sup>4</sup>	X	X	X		X		X	X	X	X	X	X	X	
Free GM-CSF, GM-CSF-GSK3196165 complex		X <sup>4</sup>	X	X	X		X		X	X	X			X	X	
PD blood biomarkers		X <sup>4</sup>			X		X				X				X	
RNA blood biomarker		X <sup>4</sup>									X			X	X	
PGx sampling DNA <sup>16</sup>		X <sup>4</sup>														
Lung biomarkers		X <sup>4</sup>									X			X	X	
Immunogenicity (anti-GSK3196165 antibody) <sup>17</sup>		X <sup>4</sup>			X		X				X			X	X	
Anti-GM-CSF auto-antibodies		X <sup>4</sup>														
Study Treatment GSK3196165/placebo <sup>18</sup>		X		X	X	X	X	X	X	X						

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

1. All subjects who withdraw from the study should have an early withdrawal (EW) visit as soon as possible after study agent discontinuation and then return for a follow-up visit (the last visit) for 10 weeks (12 weeks after last dose of study medication).
  2. The same individual (where possible) should perform all disease assessments for an individual subject.
  3. PRO assessments should be conducted before any tests, procedures, assessments or consultations, to avoid influencing the subjects' perception.
  4. Assessments may be performed up to 24 hours before dosing GSK3196165/placebo.
  5. All safety evaluations should be conducted before dosing GSK3196165/placebo.
  6. Height will be measured at only screening.
  7. Complete physical at screening, and then limited physical examination (see Section 7.4.7) thereafter.
  8. ECG should be performed before vital signs, blood draws, and dosing (triplicate ECGs required at screening, and single thereafter unless there are safety concerns, in which case repeats may be required (see Section 7.4.9)).
  9. Only SAEs related to study participation or related to a GSK product will be recorded from the time a subject consents to participate in the study.
  10. Unless performed within previous 12 weeks (No need to repeat if subject re-screened).
  11. Chest HRCT if  $D_{LCO} \geq 60\%$  -  $< 70\%$  predicted (No need to repeat if subject re-screened).
  12.  $\geq 8$  hours fasting required before blood draw.
  13. For women of child-bearing potential. S=serum; U=urine.
  14. ESR measured locally.
  15. PK sampling should be collected before dosing at the visits scheduled study treatment (GSK3196165/placebo). At the visits doesn't scheduled study treatments, it may be collected in any time during the visit. (Day 3, 74, 85, 106, 127, 155, and early withdrawal visit).
  16. In consenting subjects.
  17. In addition to these scheduled immunogenicity assessments, "event-driven" testing will also be employed for those subjects that experience anaphylaxis, serious hypersensitivity, or adverse events related to study drug administration that led to withdrawal from the study (see Section 7.5).
  18. GSK3196165 or placebo must be administered on the same day each week  $\pm 1$  day for the first 5 weekly doses, thereafter on the same day EOW  $\pm 3$  days for bi-weekly doses.
- \* The Day 3 (Visit 3) blood sample must be drawn 2 days ( $\pm 1$  day is allowable) after the first dose, and the Day 74 (Visit 11) blood sample must be drawn 3 days ( $\pm 1$  day is allowable) after the last dose.
- \*\* HBV-DNA sample will be collected from all subjects, and HBV-DNA will be tested for only subjects with HBs Ab positive.

## 7.2. Screening and Critical Baseline Assessments

After written, informed consent, 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 4 weeks of Day 1 (except for subjects being treated with azathioprine or leflunomide, where written informed consent for the study must be obtained prior to discontinuing these drugs and beginning the screening period). Women and men of reproductive potential must consent to use of a highly effective method of contraception for the period predefined in [Appendix 2](#).

- The following demographic parameters will be captured: year of birth, sex, race and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.
- Rheumatoid arthritis history – disease duration, medication history, RA functional class (I, II or III) will be confirmed.
- The following examination, confirmation and test will be conducted.
  - Physical examination (complete examination at screening, and brief examination at Day 1 visit; see Section 7.4.7).
  - Vital signs including temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
  - Triplicate 12-lead ECG (screening only).
  - Chest X-ray (posterior to anterior [PA] and lateral, or in accordance with local requirements) (screening only).
    - 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.
    - Spirometry FEV<sub>1</sub>, FVC and DLCO (see SRM for additional details) (screening only).
    - Baseline chest HRCT for subjects with DLCO values between  $\geq 60\%$  -  $< 70\%$ , and it is recommended that the subject will be reviewed by a local pulmonologist to exclude significant pre-existing respiratory disease.
  - Cough, Lung Auscultation, Pulse Oximetry, Borg Dyspnea Scale.
  - AEs reporting and recording of concomitant medications.
- Blood samples will be taken for:
  - Hematology.
  - Biochemistry.



- Serum beta subunit human chorionic gonadotropin ( $\beta$ hCG) pregnancy test (screening only).
- HIV antibody, Hepatitis B surface antigen, anti-HBc, and Hepatitis C antibody testing (screening only).
- CRP.
- ESR (baseline only).
- Cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) (baseline only).
- Autoimmune serology: RF and ACPA (i.e., anti-CCP antibodies) (screening only).
- T-spot test for TB (screening only).
- Exploratory GM-CSF, PD, lung biomarkers and anti-GM-CSF auto-antibodies (baseline only).
- PK samples and immunogenicity (anti-GSK3196165 antibody) (baseline only).
- RNA (in consenting subjects) (baseline only).
- Pharmacogenomic DNA (in consenting subjects) (baseline only).
- Urine sample will be taken for:
  - Routine urinalysis (screening only).
  - Urine  $\beta$ hCG pregnancy test (baseline only).
- Disease activity assessments (see Section 7.6) and Patient-reported outcome (PRO) questionnaires (see Section 7.9):
  - Tender joint count (68 joints).
  - Swollen joint count (66 joints).
  - Patient's Assessment of Arthritis Pain.
  - Patient's Global Assessment of Arthritis.
  - Physician's Global Assessment of Arthritis.
  - HAQ-DI.
  - FACIT-Fatigue (baseline only).

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. Pharmacokinetics

Blood samples for pharmacokinetic analysis of GSK3196165 will be collected at the time points indicated in the Time and Events Table (Section 7.1). The actual date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK

samples may be obtained at additional time points to ensure thorough PK monitoring. Details of PK blood sample collection, processing, storage and shipping procedures are provided in the SRM.

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 for samples in GSK3196165 group, but not in placebo group. Raw data will be archived at the bioanalytical site (detailed in the SRM).

PK analyses are described in Section 9.4.1 and Section 9.4.5.1.

## **7.4. Safety**

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

### **7.4.1. Study visits**

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

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

All subjects will return for a follow-up visit at 10 weeks after completion/withdrawal of treatment period. Particular attention will be paid to withdrawal symptoms given the potential risk associated with release of immune suppression.

### **7.4.2. Safety endpoints and other assessments**

- Incidence of AEs/SAEs.
- Incidence of AESI (such as serious infections and opportunistic infections) (see Section 7.4.5).
- Pulmonary events (cough, dyspnea, pulse oximetry, spirometry, DL<sub>CO</sub>).
- Lung biomarkers (such as SP-D, KL-6, cholestenic acid).
- ECG measurements.
- Vital signs.
- Hematological and clinical chemistry parameters.

- Physical examinations.
- Pregnancy test (for women of child-bearing potential).
- Immunogenicity (anti-GSK3196165 antibody).

#### **7.4.3. Adverse Events (AEs) and Serious Adverse Events (SAEs)**

The definitions of an AE or SAE can be found in [Appendix 5](#).

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

##### **7.4.3.1. Time period and Frequency for collecting AE and SAE information**

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (12 weeks after the last dose of investigational product), at the timepoints specified in the Time and Events Table (Section [7.1](#)).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24hours, as indicated in [Appendix 5](#).
- 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 5](#).

##### **7.4.3.2. Method of Detecting AEs and SAEs**

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

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

#### **7.4.3.3. 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 7.4.5) 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 4](#).

#### **7.4.3.4. Cardiovascular and Death Events**

For any cardiovascular events detailed in [Appendix 5](#) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

#### **7.4.4. 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, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

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

#### **7.4.5. AEs 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.

#### **7.4.5.1. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**

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

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

These DREs will be monitored by a Safety Review Team (SRT) on a routine basis.

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

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

*OR*

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

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

#### **7.4.5.2. 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 GSK3196165 IB and will notify the IRB/IEC, if appropriate according to local requirements.

#### **7.4.6. Pregnancy**

- Any pregnancy (participating females and female partners of participating males) that occurs from first administration of investigational product to the follow-up visit must be reported.
- 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 6](#).

#### **7.4.7. Physical Exams**

- A complete physical examination at the Screening visit will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination at subsequent assessments will be performed as indicated in the Time and Event Table (Section [7.1](#)) and include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Body weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

#### **7.4.8. 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 after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.
- A single set of values will be collected and recorded in the source documentation and eCRF.

#### **7.4.9. Electrocardiogram (ECG)**

- Triplicate 12 lead ECGs will be obtained at screening, then single 12 lead ECGs will be obtained 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., 5-10minutes). Refer to Section [5.4.2](#) for QTc withdrawal criteria and additional QTc readings that may be necessary.

#### 7.4.10. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in [Table 3](#), must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Section [7.1](#)). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Central Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

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

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

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in [Table 3](#).

**Table 3 Routine Laboratory Assessments**

Hematology	Biochemistry	Urinalysis
Hemoglobin	Sodium	Urine dipstick
Hematocrit	Potassium	Glucose
Mean corpuscular volume (MCV)	Calcium	Protein
Mean corpuscular hemoglobin (MCH)	Phosphate	
Mean corpuscular hemoglobin concentration (MCHC)	Urea nitrogen	Microscopy of urine sediment for erythrocytes, leukocytes and casts if urine dipstick abnormal
Erythrocyte count	Creatinine	
Reticulocyte count	Creatinine clearance (calculated)	
Leukocyte count	Aspartate transaminase (AST)	
Leukocyte differential count	Alanine transaminase (ALT)	
neutrophils	γ-glutamyl transpeptidase (GGT)	
eosinophils	Lactate dehydrogenase (LDH)	Urine pregnancy test
basophils	Alkaline phosphatase (ALP)	
monocytes	Bilirubin (total)	
lymphocytes	Creatine Phosphokinase (CPK)	
Platelets	Total protein	
Activated partial thromboplastin time (aPTT)		
Prothrombin Time (PT)		

Hematology	Biochemistry	Urinalysis
International Normalised Ratio (INR) Fibrinogen Erythrocyte Sedimentation Rate (ESR)*	Albumin Albumin/globulin ratio Glucose C-reactive protein (CRP) Cholesterol** Triglycerides** High-density lipoprotein (HDL)** Low-density lipoprotein (LDL)**  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 and cholestenolic acid (see Section 7.7). Baseline measurement of GM-CSF autoantibodies will be measured.

#### 7.4.11. 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 (FEV<sub>1</sub>, FVC), gas transfer (D<sub>LCO</sub>)

Further details of this assessment are provided 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), the subject should 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.

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.

## **7.5. Immunogenicity**

Serum samples will be collected and tested for presence of antibodies that bind to GSK3196165. Serum samples for testing anti-GSK3196165 antibodies will be collected as described in Section 7.1, Time and Events Table. 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 Study Reference Manual (SRM).

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

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

## **7.6. Efficacy**

Efficacy assessments will include:

- Evaluation of all 68 joints for tenderness and 66 joints for swelling to be performed by an independent joint evaluator.
- VAS (global disease) for the subject and treating physician.
- VAS (pain) for the subject.

- Health assessment questionnaire – disability index (HAQ-DI), as well as other PRO assessments described in more detail in Section 7.9.
- Laboratory assessments (CRP, ESR).

Based on these assessments DAS28(CRP), ACR (20, 50 and 70), the EULAR response, SDAI and CDAI will be calculated.

### **7.6.1. Joint Assessments**

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

#### **7.6.1.1. Excluded from Joint Assessments**

Replaced or fused joint will not be included in joint evaluations. In addition, if the subjects who has had an intra-articular corticosteroid injection, that joint will not be included in joint evaluation at Week 12. The reason for absence of the evaluations of those joints must be recorded.

#### **7.6.1.2. Independent Joint Evaluator**

One or more independent assessors, who have experience in performing joint assessments, will be designated at each trial site to perform joint assessments. Preferably the same independent assessor will perform all joint assessment for the same subject throughout the trial. The principal investigator must ensure that the independent joint assessor can perform joint assessment properly. This also applies if the independent joint assessor is replaced during the trial.

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

### **7.6.2. Patient's Assessment of Arthritis Pain**

Subjects will assess the severity of their current arthritis pain using a 10 unit visual analog scale (VAS) by placing a mark on the scale between “0” (no pain) and “10” (most severe pain), which corresponds to the magnitude of their current pain.

Subjects will also assess the severity of their past week's arthritis pain using a 100 unit visual analog scale (VAS) by placing a mark on the scale between “0” (no pain) and “100” (severe pain), which corresponds to the magnitude of their pain for the past week.

Further details of this assessment are provided in the SRM.

### **7.6.3. Patient's Global Assessment of Arthritis**

Subjects will complete a global assessment of disease activity using the patient global assessment (PtGA) visual analog scale, a VAS with anchors “0” (very well) to “10” (very poor).

Further details of this assessment are provided in the SRM.

#### 7.6.4. Physician's Global Assessment of Arthritis

Physicians will complete a global assessment of disease activity using the physician global assessment item (PhGA), a VAS with anchors "0" (none) to "10" (extremely active), respectively.

Further details of this assessment are provided in the SRM.

#### 7.6.5. DAS Assessments

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

The components of the DAS 28 arthritis assessment include:

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

Sites/investigators will not have access to ongoing DAS scores, apart from the screening results (needed to confirm eligibility).

The DAS28 score is calculated using the following formula, where TJC = tender joint count, SJC = swollen joint count, PtGA = patients global assessment (mm), CRP = C-reactive protein (mg/L) and ESR = Erythrocyte sedimentation rate (mm/hr):

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

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

##### 7.6.5.1. Disease activity criteria based on DAS28 score

The disease activity is classified into the below 4 categories based on the calculated DAS 28 score. Remission is achieved by a DAS28 score lower than 2.6.

DAS28 score	Categories
>5.1	High disease activity
≥3.2~≤5.1	Moderate disease activity
<3.2	Low disease activity
<2.6	Remission

### 7.6.5.2. EULAR response criteria based on DAS28 score

The EULAR response criteria based on DAS 28 score are used to assess the response of the disease activity.

DAS28 score at timepoints	Change from baseline (Day 1) in DAS 28		
	>1.2	>0.6 ~ ≤1.2	≤0.6
<3.2	Good	Moderate	None
≥3.2 ~ ≤5.1	Moderate	Moderate	None
>5.1	Moderate	None	None

### 7.6.6. ACR Assessments

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

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

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

### 7.6.7. SDAI and CDAI

The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are assessment methods for the disease activity and are determined using more simple formula than DAS28. These score will be calculated at each assessment timepoint.

The components of the SDAI and CDAI score include:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).

- CRP (Only SDAI).
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.

The SDAI and CDAI score are calculated using the following formula, where TJC = tender joint count, SJC = swollen joint count, PtGA = patients global assessment (cm) and PhGA = physicians global assessment (cm):

$$\text{SDAI} = \text{SJC28} + \text{TJC28} + \text{PtGA}/10 + \text{PhGA}/10 + \text{CRP (mg/dl)}$$

$$\text{CDAI} = \text{SJC28} + \text{TJC28} + \text{PtGA}/10 + \text{PhGA}/10$$

### 7.7. Biomarker(s)/Pharmacodynamic Markers

Blood samples for biomarker/pharmacodynamic analysis will be collected at the time points indicated in the Time and Events Table (Section 7.1). 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 SRM. 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.

The following biomarkers/pharmacodynamic endpoints will be assessed:

- Target engagement: analysis of free soluble GM-CSF and soluble GM-CSF complexed to GSK3196165.
- Soluble biomarkers which may be predictive of response to GSK3196165 such as MRP8/14, ARG5 neopeptide, YKL-40 and 14-3-3 $\eta$ .
- Serum cytokines to monitor mechanism of action of GSK3196165 such as IL-6, IL-1 $\beta$ , TNF $\alpha$ , IL-17A and IL-17F.
- Safety biomarkers which may be predictive of lung damage including the following: SP-D, KL-6, cholestenic acid and measurement of GM-CSF autoantibodies at baseline.
- These will be analysed at the end of the study or in the event of a pulmonary safety signal which would require further investigation.

Additional exploratory biomarkers in the blood/serum (RNA) will be collected from only consenting subjects and may include but will not be limited to the following:

- RNA analysis of blood.

### 7.8. Pharmacogenetics

Information regarding pharmacogenetic (PGx) is included in [Appendix 7](#).

## 7.9. Value Evidence and Outcome

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.

### 7.9.1. HAQ-DI

The functional status of the subject will be assessed by means of the Disability Index of the Health Assessment Questionnaire (HAQ-DI) (see Appendix 6). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas[Fries, 1980; Matsuda, 2003] :

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

### 7.9.2. FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) -Fatigue questionnaire is a patient-reported measure validated and developed originally to assess fatigue in individuals with cancer (see Appendix 6). The FACIT-fatigue has subsequently been used and validated in numerous chronic conditions, including RA.

## 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

A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP). Any deviations from the analyses described in the protocol will be documented in the RAP or the final study report.

## 9.1. Hypotheses

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

## 9.2. Sample Size Assumptions

The sample size is determined based on feasibility. A total of 40 subjects will be randomized in a 1:1:1:1 proportion to receive GSK3196165 doses of 45 mg, 90 mg, 180 mg or placebo.

Table 4 provides the precision of percentage of subjects with specific adverse events in each group with 10 subjects.

**Table 4 Precision of percentage of subjects with specific adverse events in each group with 10 subjects**

Number of subjects	Number of particular safety events observed	Exact 95% confidence intervals
10	1	0.3% - 44.5%
10	2	2.5% - 55.6%
10	3	6.7% - 65.2%

## 9.3. Data Analysis Considerations

### 9.3.1. Analysis Populations

- All Screening Population: The All Screening Population consists of all subjects who are given subject number and whose data including demographics are collected at screening.
- Randomized population: The randomized population is defined as all subjects who were randomized to treatment regardless of whether they actually receive study treatment.
- Intention to Treat (ITT) Population: The ITT Population consists of all randomized subjects who receive at least one dose of study treatment. This population will be used for efficacy and safety analyses.
- Pharmacokinetic (PK) population: The PK Population consists of all GSK3196165-treated subjects from whom PK samples are collected and analyzed.

Additional populations may be defined in the RAP.

### **9.3.2. Interim Analysis**

No interim analysis in midstream of the treatment period is planned. However once all subjects have completed visits in the treatment period, an interim analysis may be performed to discuss within GSK and consult with the regulatory authority on the future development plan of GSK3196165. In that case all data up to the end of treatment period for each subject will be frozen and then the randomization schedule will be unblinded for the analysis.

## **9.4. Key Elements of Analysis Plan**

### **9.4.1. Primary Analyses**

For serum concentrations of GSK3196165 over time, individual data will be listed and presented in graphical form, and summary statistics at each time point will be calculated by each dose level. The following PK variables will be derived as data allowed: C<sub>max</sub>, t<sub>max</sub>, AUC<sub>tau</sub>, AUC(0-inf), and t<sub>1/2</sub>. For PK parameters, summary statistics will be calculated by each dose level, and scatter plots against the dose level will be generated. Dose proportionality will also be assessed with the power model.

A population pharmacokinetic modeling approach may be further applied to model the drug concentration data obtained in the study in the future. Further details of population pharmacokinetic analyses will be described in a separate Reporting and Analysis Plan (RAP) if population PK analyses is performed.”

### **9.4.2. Safety Analyses**

All adverse events will be coded using MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of subjects with any adverse events will be summarized by dose. The study treatment-related AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be reported separately.

For other safety parameters, such as laboratory assessment, vital signs, 12-lead ECG, and anti-GSK3196165 antibody, safety biomarkers, data and/or change from baseline will be summarized with descriptive statistics at each assessment visit by dose.

### **9.4.3. Immunogenicity Analyses**

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

### **9.4.4. Efficacy Analyses**

The ITT population with observed case dataset will be used for efficacy analyses. Time course of the change from baseline in DAS28(CRP) will be analyzed by mixed model for repeated measurements (MMRM). The dose response analyses will be performed on the change from baseline in DAS28(CRP) at Week 12. Full details for all efficacy analyses will be given in the RAP.



#### **9.4.5. Biomarker(s)/Pharmacodynamic Marker(s) Analyses**

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

##### **9.4.5.1. Pharmacokinetic/Pharmacodynamic Analyses**

Exploratory plots will be presented for individual and/or pooled plasma GSK3196165 concentrations versus pharmacodynamic markers or efficacy endpoints. If data permit, potential association between systemic exposure of GSK3196165 and identified pharmacodynamic markers (e.g. CRP, MRP8/14) and efficacy endpoints (e.g. change in DAS28(CRP) score from baseline) will be explored. More details are included 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 will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable).
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC).
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- 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 Publicly 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 1: Abbreviations and Trademarks

#### Abbreviations

ACPA	Anti-cyclic citrullinated protein antibody
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BCG	Bacillus Calmette-Guérin
βhCG	Human chorionic gonadotropin β-subunit
CCP	Cyclic citrullinated peptide
CD	Cluster of differentiation antigen
CDAI	Clinical disease activity index
CIA	Collagen-induced arthritis
C <sub>max</sub>	Maximum concentration
C <sub>min</sub>	Minimum concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRP	C-reactive protein
csDMARD	Conventional synthetic disease modifying antirheumatic drugs
CT	Computer Tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P
DAS	Disease activity score
DAS28	Disease activity score for 28 different joints
D <sub>LCO</sub>	Diffusing capacity of the lung for carbon monoxide
DMARD	Disease modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
DRE	Disease-related event
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FACIT-Fatigue	Functional assessment of chronic illness therapy-Fatigue
FDA	Food and Drug Administration
FEV <sub>1</sub>	Forced expiratory volume in one second
FRP	Females of reproductive potential
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity

GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	$\gamma$ -glutamyltranspeptidase
GM-CSF	Granulocyte-macrophage colony stimulating factor
GSK	GlaxoSmithKline
GSKDrug	GSKDrug
HAQ-DI	Health Assessment Questionnaire Disability Index
HBc	Hepatitis B virus core
HBs	Hepatitis B virus surface
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human lymphocyte antigen
HPLC	High performance liquid chromatography
HRCT	High-resolution computed tomography
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INR	International normalized ratio
ITT	Intent to Treat
JAK	Janus kinase
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSDS	Material Safety Data Sheet
MTX	Methotrexate
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PA	Posterior to anterior
PAP	Pulmonary alveolar proteinosis

PCR	Polymerase chain reaction
PCP	Pneumocystis pneumonia
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetics
PRO	Patient- reported outcome
PT	Prothrombin time
QTcF	QT intervals corrected by Fridericia's formula
RA	Rheumatoid arthritis
RAP	Reporting and analysis plan
RF	Rheumatoid factor
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous
SDAI	Simple disease activity index
SE	Sentinel event
SP-D	Surfactant D
SRM	Study Reference Manual
SRT	Safety Review Team
t1/2	Elimination half-life
tmax	Time to maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale

### Trademark Information

<b>Trademarks of the GlaxoSmithKline group of companies</b>
NONE

<b>Trademarks not owned by the GlaxoSmithKline group of companies</b>
InForm
MedDRA

## 12.2. Appendix 2: Contraception eligibility criteria for female and male subjects

### 12.2.1. Female

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

1. 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.
2. 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.

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

The list does not apply to FRP with same sex partners, 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.

- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Combined estrogen and progestogen oral contraceptive [[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. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

If using hormonal contraceptives, including oral, injections, implants, and patches, a secondary method of contraception must be used.

### **12.2.2. Male**

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.
- b) Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
  - Intrauterine device or intrauterine system
  - Combined estrogen and progestogen oral contraceptive [[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 from the time of first dose of study medication until 12 weeks after the last dose of study medication.

### **Reference:**

Hatcher RA, Trussell J, Nelson AL, et al. *Contraceptive Technology. 20th edition.* Atlanta, Georgia:Arden Media, 2011:50. Table 3.2.

### 12.3. Appendix 3: Liver chemistry stopping criteria and required follow up assessments

**Phase II liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

#### Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
<b>ALT-absolute</b>	ALT $\geq$ 5xULN
<b>ALT Increase</b>	ALT $\geq$ 3xULN persists for $\geq$ 4 weeks
<b>Bilirubin<sup>1,2</sup></b>	ALT $\geq$ 3xULN <b>and</b> bilirubin $\geq$ 2xULN (>35% direct bilirubin)
<b>INR<sup>2</sup></b>	ALT $\geq$ 3xULN <b>and</b> INR>1.5, if INR measured
<b>Cannot Monitor</b>	ALT $\geq$ 3xULN <b>and</b> cannot be monitored weekly for 4 weeks
<b>Symptomatic<sup>3</sup></b>	ALT $\geq$ 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
<ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study treatment</li> <li>• Report the event to GSK <b>within 24 hours</b></li> <li>• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE<sup>2</sup></li> <li>• Perform liver event follow up assessments</li> <li>• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> <li>• <b>Do not restart/rechallenge</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is</b> granted</li> <li>• If restart/rechallenge <b>not allowed per protocol or not granted by GSK</b></li> </ul>	<ul style="list-style-type: none"> <li>• Viral hepatitis serology<sup>4</sup></li> <li>• Blood sample for pharmacokinetic (PK) analysis, obtained less than 12 weeks after last dose<sup>5</sup></li> <li>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>• Fractionate bilirubin, if total bilirubin<math>\geq</math>2xULN</li> <li>• Obtain complete blood count with differential to assess eosinophilia</li> <li>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</li> </ul>

<p><b>Medical Governance</b>, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments</p> <p><b>MONITORING:</b></p> <p><b><u>For bilirubin or INR criteria:</u></b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24 hrs</b></li> <li>Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>For All other criteria:</u></b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24-72 hrs</b></li> <li>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</li> </ul>	<ul style="list-style-type: none"> <li>Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications</li> <li>Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>For bilirubin or INR criteria:</u></b></p> <ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)</li> <li>Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009])</li> <li>Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms</li> </ul>
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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  $\geq$  3xULN **and** bilirubin  $\geq$  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  $\geq$  3xULN and bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  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 or Hepatitis E RNA.
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.

### Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
ALT $\geq 3 \times$ ULN and $< 5 \times$ ULN and bilirubin $< 2 \times$ ULN, <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 4 weeks.	<ul style="list-style-type: none"> <li>• Notify the GSK medical monitor <b>within 24 hours</b> of learning of the abnormality to discuss subject safety.</li> <li>• Subject can continue study treatment.</li> <li>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline.</li> <li>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above.</li> <li>• If, after 4 weeks of monitoring, ALT <math>&lt; 3 \times</math>ULN and bilirubin <math>&lt; 2 \times</math>ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</li> </ul>

#### References

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Protein Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos.* 2009;37:1779-84.



## 12.4. Appendix 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 meeting AE definition include:

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

#### Events NOT 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.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- 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 fulfills 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

<p>normal life functions.</p> <ul style="list-style-type: none"> <li>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.</li> </ul>
Is a congenital anomaly/birth defect
<p>Other situations:</p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>
<p>Is associated with liver injury and impaired liver function defined as:</p> <ul style="list-style-type: none"> <li>ALT <math>\geq</math> 3xULN and total bilirubin* <math>\geq</math> 2xULN (&gt;35% direct), or</li> <li>ALT <math>\geq</math> 3xULN and INR** &gt; 1.5.</li> </ul> <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT <math>\geq</math> 3xULN and total bilirubin <math>\geq</math> 2xULN, then the event is still to be reported as an SAE.</p> <p>** 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.</p>

### 12.4.3. Recording of AEs and SAEs

AEs and SAE Recording:
<ul style="list-style-type: none"> <li>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.</li> <li>The investigator will then record all relevant information regarding an AE/SAE in the CRF.</li> <li>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 CRF page.</li> </ul>

- 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.

#### 12.4.4. 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 Investigator Brochure (IB) 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 CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

#### 12.4.5. 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 PV Information Management Service department.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- 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 to the PV Information Management Service department.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Medical Monitor /Sponsor Contact Information page.

#### 12.4.6. 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.

### 12.4.7. Definition of Cardiovascular Events

#### Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF 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

## 12.5. Appendix 5: Collection of Pregnancy Information

### 12.5.1. Female

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this 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 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. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed 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.



## **12.7. Appendix 7: Country Specific Requirements**

### **12.7.1. Study Conduct Considerations**

#### **12.7.1.1. Regulatory and Ethical Considerations**

The study will be conducted in accordance with “the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)” and the Pharmaceutical Affairs Law. GSK will submit the CTN to the regulatory authorities in accordance with the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

#### **12.7.1.2. Informed Consent**

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject of the study including the written information. The investigator (or subinvestigator) should provide the subject ample time and opportunity to inquire about details of the study. The subject should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

#### **12.7.2. Study Period**

December 2016 ~ January 2018

#### **12.7.3. Study Administrative Structure**

Sponsor information is included in Exhibit 1. List of Medical Institutions and Investigators is included in Exhibit 2.

#### **12.7.4. Pharmacogenetics**

##### **Background**

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [[Gorin, 2012](#)] with certain variants reported to influence treatment response [[Chen, 2012](#)]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the

development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

### **Pharmacogenetic Research Objectives and Analyses**

The objective of the pharmacogenetic (PGx) research is to understand the relationship between genetic factors and response to GSK3196165. To achieve this objective, the relationship between genetic variants and the followings are investigated.

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

PGx data may be generated while the study is underway or following completion of the study. PGx evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). PGx 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 PGx investigations will be reported either as part of the clinical RAP and study report, or in a separate pharmacogenetic RAP and report, as appropriate.

### **Study Population**

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

### **Study Assessments and Procedures**

A key component of successful PGx research is the collection of samples during clinical studies. Collection of samples, even when no a priori hypothesis has been identified, may enable future PGx analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for PGx research. Instructions for collection and shipping of the PGx 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 PGx 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 PGx research may still participate in the study. PGx informed consent must be obtained prior to any blood being taken.

### **Subject Withdrawal from Study**

If a subject who has consented to participate in PGx 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 PGx sample, if already collected:

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

If a subject withdraws consent for PGx 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 PGx research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- PGx 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 PGx 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 PGx 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 PGx Data**

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

GSK may share PGx research data (after deleting the subject number so that the provided information will not be identified) 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 PGx 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.

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## **12.8. Appendix 8: Protocol Changes**

### **Protocol Amendment: 01**

#### **4.6.1.Risk Assessment, Infections, Mitigation Strategy**

Added the below sentence in Subject monitoring section.

1. When subjects are considered to be at high risk of pneumocystis pneumonia (PCP) after the initiation of treatment by the investigator's judgement, a preventive dose of co-trimoxazole is permitted.

#### **Rationale**

As Japanese RA subjects treated with biologics may be more susceptible to PCP, a preventive dose of co-trimoxazole is allowed to ensure the safety of subjects considered as high risk of PCP, according to PMDA requests.

#### **5.1.Inclusion Criteria, 13**

Criteria for FVC  $\geq 80\%$  predicted added as below.

13.D<sub>LCO</sub>  $\geq 60\%$  predicted; forced expiratory volume in 1 second (FEV<sub>1</sub>)  $\geq 70\%$  predicted; forced vital capacity (FVC)  $\geq 80\%$  predicted.

#### **Rationale**

FVC criteria was added in Inclusion Criteria to exclude asymptomatic interstitial pneumonia.

#### **5.2.Exclusion Criteria, 25**

Added criteria for HBV-DNA for the subjects with positive anti-HBs antibody as below.

25.Serologic evidence of current/previous Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg) and anti-Hepatitis B core (anti-HBc) antibody as follows within 4 weeks of Day 1.

2. Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
3. Subjects with positive anti-HBs antibody and HBV-DNA ( $\geq 2.1$  log copies/mL) are excluded.

#### **Rationale**

According to the treatment guideline of HBV infection, the HBs antibody positive subjects require HBV-DNA testing, and will be randomised once HBV-DNA ( $< 2.1$  log copies/mL) is confirmed.

#### **5.4. Withdrawal/Stopping Criteria**

Added HBV-DNA stopping criteria.

4. Detected ( $\geq 2.1$  log copies/mL) HBV DNA for subjects who have positive anti-HBs antibody.

#### **Rationale**

HBV-DNA stopping criteria was clarified for subjects with positive anti-HBs antibody.

#### **6.10.2. Prohibited Medications and Non-Drug Therapies, 6.10.2.2. Related to Methotrexate**

Allowed a preventive dose of co-trimoxazole for subjects considered at high risk of PCP.

5. Concomitant administration of folate antagonists such as co-trimoxazole\* (trimethoprim-sulfamethoxazole), triamterene and nitrous oxide are prohibited.

\*: When a preventive dose is required for subjects considered at high risk of pneumocystis pneumonia (PCP) after the initiation of treatment by the investigator's judgement, the approved low dose of co-trimoxazole is allowed (1 tablet daily or 3 times a week).

#### **Rationale**

A preventive dose of TMP-SMX is allowed to ensure the safety of subjects with high risk of PCP, according to PMDA requests.

#### **7.1. Time and Events Table**

Changed HBV-DNA test at Screening, and added footnote as below.

\*\* HBV-DNA sample will be collected from all subjects, and HBV-DNA will be tested for only subjects with HBs Ab positive.

#### **Rationale**

To confirm the existing of HBV-DNA for HBs antibody positive subjects at Screening.

#### **7.6.2. Patient's Assessment of Arthritis Pain and 12.6. Appendix 6: Assessment of Safety, Efficacy, Value Evidence and Outcome, 12.6.2. Efficacy**

Added "Past week's pain" VAS assessment.

#### **Rationale**

"Past week's pain" assessment sheet was added in protocol.

### 9.3.1. Analysis Populations

Analysis populations were revised as below.

- All Screening Population: The All Screening Population consists of all subjects who are given subject number and whose data including demographics are collected at screening.
- Randomized population: The randomized population is defined as all subjects who were randomized to treatment regardless of whether they actually receive study treatment.
- Intention to Treat (ITT) Population: The ITT Population consists of all randomized subjects who receive at least one dose of study treatment. This population will be used for efficacy and safety analyses.
- Pharmacokinetic (PK) population: The PK Population consists of all GSK3196165-treated subjects from whom PK samples are collected and analyzed.

#### Rationale

To be consistent with on-going global Phase IIb study (201755).

### 12.2. Appendix 2: Contraception eligibility criteria for female and male subjects, 12.2.1. Female and 12.2.2. Male

Removed the following contraception methods.

- Contraceptive subdermal implant
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

#### Rationale

These contraception methods are not approved in Japan.

#### Protocol Amendment: 02

##### 5.1. Inclusion Criteria

Changed the CRP criterion from  $\geq 0.5$  mg/dL to  $\geq 0.3$  mg/dL.

7. C-Reactive Protein (CRP)  $\geq 0.3$  mg/dL at screening.

#### Rationale

To allow the patients with 0.3 ~ 0.5 mg/dL CRP in the study.