TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	A multi-centre Phase IIa double-blind, placebo-controlled study to investigate the efficacy and safety of GSK3196165 in subjects with inflammatory hand osteoarthritis.

Compound Number: GSK3196165

Development Phase: IIa

Effective Date: 03-JAN-2017

Protocol Amendment Number: 2

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N242468_00	2015-AUG-14	Original
2015N242468_01	2015-NOV-16	Amendment No. 1
Correction of contraceptive requirements in Appendix 5, in response to regulatory review comments. Minor correction of question number in post-treatment interview guidance.		
2015N242468_02	2017-JAN-03	Amendment No. 2
Amendment of inclusion criteria, #2, #3 and #5, clarification of exclusion criteria #9 and amendment of exclusion criteria #19(d). Addition of two planned interim analyses to Section 9.3 and associated update to study blinding details (Section 6.4). Addition of two PK sample time points (one on Day 85 and one on Day 155). Further minor corrections and clarifications to wording throughout the protocol. See Appendix 14 for full details.		

SPONSOR SIGNATORY:

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3 Jan '17
Date

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

Regulatory Agency Identifying Number(s):

EudraCT number – 2015-003089-96

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204851

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204851

Rationale

This study is designed to investigate whether GSK3196165 may offer a treatment benefit for subjects with inflammatory hand osteoarthritis (HOA).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To assess the efficacy potential of GSK3196165 on pain in inflammatory HOA.	• Change from baseline in 24h average hand pain intensity at Week 6, as measured by daily pain Numerical Rating Scale (NRS) averaged over the 7 days prior to assessment visit.
Secondary	
• To evaluate impact of GSK3196165 on average and worst HOA pain, over time.	• Change from baseline in 24h average hand pain intensity at each visit, measured by daily pain NRS and averaged over the 7 days prior to each assessment visit. • Change from baseline of worst hand pain intensity over 24h at each visit, measured by daily NRS and averaged over the 7 days prior to each assessment visit. • Proportion of subjects in each treatment group achieving a 30% reduction in 24h average hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit. • Proportion of subjects in each treatment group achieving a 50% reduction in 24h average hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit. • Proportion of subjects in each treatment group achieving a 30% reduction in 24h worst hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit. • Proportion of subjects in each treatment group achieving a 50% reduction in 24h worst hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit.
• To assess the impact of GSK3196165 on hand pain (on use), stiffness and function, over time.	• Change from baseline in Australian Canadian Hand Osteoarthritis Index (AUSCAN) 3.1 NRS, total and domains (pain, morning stiffness, function) scores at each visit.

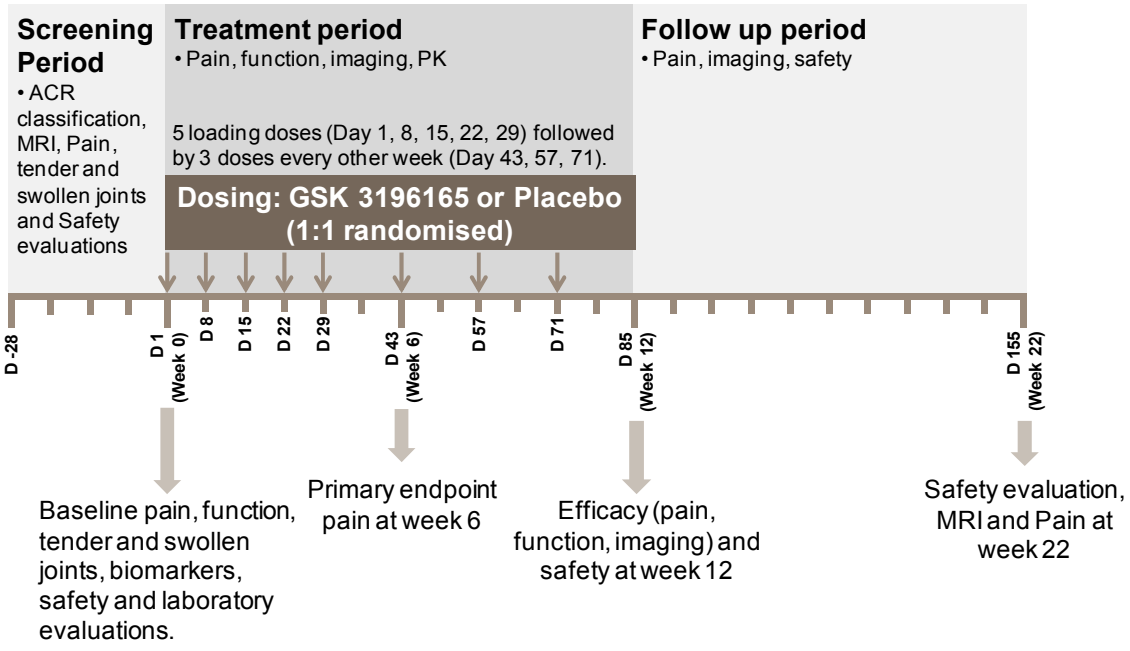
Objectives	Endpoints
• To assess the impact of GSK3196165 on HOA inflammation	• Change in number of swollen and tender hand joints at each visit.
• To assess potential impact of GSK3196165 on disease activity in HOA,	• Change from baseline in patient global assessment (PtGA) and physician global assessment (PhGA) of disease activity at Week 6,12 and 22.
• To assess safety of GSK3196165 in HOA patients, over the study duration.	• Incidence of adverse events and serious adverse events. • Incidence of infections. • Incidence of pulmonary events (cough/dyspnea, PAP and D_{LCO}). • Immunogenicity.
• To assess population pharmacokinetics of GSK3196165 in HOA.	• Population pharmacokinetics endpoints such as CL/F, Vss/F, Ka.

* If only one hand is affected by HOA and meets the inclusion criteria, the affected hand will be documented at screening and used for all assessments. In cases where both hands are affected by HOA and both meet the inclusion criteria, then the dominant hand will be documented at screening and this hand will be used for all single-hand assessments throughout the study.

Overall Design

This is a randomized Phase IIa, multicentre, double-blind, placebo-controlled parallel group study with the primary objective to assess the efficacy potential of GSK3196165 on pain, in subjects with active inflammatory HOA.

Study schematic



Treatment Arms and Duration

- A screening period of up to 4 weeks, will be followed by a 12 week treatment period (dosing with GSK3196165 or placebo) then a follow up period, completing on week 22. The total study duration for an individual subject will be approximately 26 weeks.
- The Study consists of 2 arms: treatment with GSK3196165 or placebo will be given as a single subcutaneous injection (shielded to subjects) to the abdomen or thigh, by an unblinded administrator weekly for 5 injections, from Week 0 to Week 4 (Days 1, 8, 15, 22, 29), then every other week for 3 further injections, from Week 6 until Week 10 (Days 43, 57 and 71).
- In total, each subject will receive up to 8 doses of study treatment.

Type and Number of Subjects

Approximately 40 subjects with active inflammatory HOA who have passed all screening assessments, will be enrolled onto the study. At least 40 subjects will be randomized across the two treatment arms, to either placebo or GSK3196165, in a 1:1 ratio (n=20 per arm).

Analysis

- The study will test the null hypothesis that there is no difference between GSK3196165 and placebo in the change from baseline in the 24h average Pain Numerical Rating Scale (NRS) at Week 6 versus the alternative hypothesis that there is a difference between GSK3196165 and placebo in the change from baseline in the 24h average Pain NRS at Week 6 using a two-sided test.
- The primary endpoint of the study is change from baseline in 24h average hand pain intensity at Week 6, as measured by daily pain Numerical Rating Scale (NRS) averaged over the 7 days prior to assessment visit.
- The primary endpoint will be analysed using a repeated measures model (MMRM) adjusted for baseline pain score, treatment group, visit and the visit by treatment group interaction as fixed effects, patient as a random effect and day within patient as a repeated effect, using an unstructured covariance matrix.

2. INTRODUCTION

GSK3196165 is a novel human monoclonal antibody which inhibits granulocyte-macrophage colony stimulating factor (GM-CSF) and is being developed for the treatment of rheumatoid arthritis (RA) and other inflammatory diseases.

2.1. Study Rationale

This study is designed to investigate whether GSK3196165 may offer a treatment benefit for subjects with inflammatory hand osteoarthritis.

2.2. Brief Background

2.2.1. Hand osteoarthritis

Hand osteoarthritis (HOA) is the second most common form of osteoarthritis (OA) which is itself, the most common musculoskeletal disorder. The factors underlying the relationship between inflammatory and erosive HOA are not fully understood, though it seems likely that erosions could be a consequence of chronic inflammation. The presentation of HOA is typically with symptoms reflecting underlying inflammation in the proximal joints of the hand affecting the synovium, cartilage and bone. Severe hand pain can significantly impair day to day activities through functional impairment in the form of stiffness, reduced grip strength, reduced hand mobility, and difficulty performing dexterous tasks. Some patients have demonstrable bony erosions on X-Ray or Magnetic Resonance Imaging (MRI) [Kortekaas, 2015 and Kwok, 2011]. Erosive disease has the potential to irreversibly destroy joint architecture and result in permanent disability.

Treatment options for both inflammatory and erosive HOA are limited and are focused on alleviating symptoms through pain medication, local steroid injections and surgical intervention but provide limited, if any, benefit.[Gelber, 2015; Chevalier, 2014; Bijlsma, 2011; Altman, 2010 and Towheed, 2005] Hence there is a clear unmet need to develop new therapeutics which not only address symptoms but also result in disease modification such as reduction in structural joint damage or prevention of inflammatory changes in the joints which can lead to deterioration of long term functional ability.

2.2.2. GM-CSF and OA

The pathogenic characteristics of OA are loss of cartilage with associated underlying bony changes consisting of sclerosis, sub-chondral bone collapse, bone cysts and osteophyte formation [Iannone, 2003]. Pain is one of the most important symptoms of OA as it causes a significant impairment in function. The etiology of OA is likely to be multifactorial, and recent histological evidence indicates that synovitis is an early feature in OA, even in joints where it could not be detected clinically [Spector, 1997; Sowers, 2002; Haywood, 2003], with a mixed inflammatory infiltrate consisting mainly of macrophages and with pro-inflammatory mediator production (e.g. TNF, IL-1b) [Farahat, 1993; Bondeson, 2010]. It has been argued that OA synovial inflammation is qualitatively similar to that in RA, differing only in magnitude [Haraoui, 1991].

Granulocyte-macrophage colony stimulating factor receptor (GM-CSFR) is expressed in OA synovium [Berenbaum, 1994] and is spontaneously produced by OA synovial cell cultures over a time course of 5 days [Haworth, 1991]. GM-CSF induces the proliferation and activation of macrophage lineage cells leading to strongly increased production of key proinflammatory cytokines (including TNFα, IL-6, and IL-1), chemokines and matrix degrading proteases [Fleetwood, 2007; Gasson, 1991; Hamilton, 2004; Hamilton, 2013; Hart, 1991; Mantovani, 2007]. GM-CSF also serves as a differentiation factor for dendritic cells and induces upregulation of human lymphocyte antigen (HLA) class II on antigen presenting cells, which in turn will activate CD4+ T cells. In addition, GM-CSF is a strong chemo-attractant factor for neutrophils and induces the release of activated oxygen species from neutrophils, which can directly damage cartilage structure [Dang, 1999; Gomez-Cambronero, 2003]. Furthermore, it has been demonstrated pre-clinically

that GM-CSF is linked to the development of experimental [Cook, 2012] and spontaneous osteoarthritis [Stone, 2015] and it is associated with pain, function, matrix degrading proteases and structural disease severity [Cook, 2012]. Importantly, GM-CSF neutralization by a therapeutic monoclonal antibody rapidly and completely abolished existing arthritic pain and suppressed the degree of arthritis development in the collagenase induced model of OA.

Taken together, pre-clinical and clinical data suggest that blocking GM-CSF should interfere with several pathophysiological pathways and significantly reduce inflammation by inhibiting activation of inflammatory cells within the OA joint and by blocking the chemotaxis recruitment of such non-resident inflammatory cells, thus leading to a benefit on inflammatory pain and inhibiting bone and cartilage destruction.

2.2.3. GSK3196165

GSK3196165 is a high-affinity recombinant human monoclonal antibody (mAb) that binds specifically to human GM-CSF and neutralises its biological function by blocking the interaction of GM-CSF with its cell surface receptor [Steidl, 2008]. This results in an anti-inflammatory and anti-nociceptive effect in addition to affecting bone metabolism through the Receptor Activator of Nuclear factor-κB ligand (RANKL) pathway and may therefore be a viable treatment option for inflammatory HOA [Cook, 2013].

Detailed information relating to non-clinical pharmacology, safety pharmacology, pharmacokinetics and metabolism, toxicology and other pre-clinical and clinical data with GSK3196165 can be found in the GSK3196165 Investigator's Brochure (IB) and supplement [GSK Document Number 2014N190256_00 and GSK Document Number 2015N226819_00].

2.2.4. Clinical Data

GSK3196165 has been studied in 4 clinical trials to date as summarised in the IB [GSK Document Number 2014N190256_00]. In addition, a Phase IIb, double-blind, placebo controlled, dose adaptive study in 210 subjects with active moderate-severe rheumatoid arthritis despite treatment with methotrexate [GSK Document Number 2014N210890_04] has been initiated in several countries.

MSC-1001 was a Phase1b/2a multi-center, randomized, sequential group, double-blind, placebo-controlled study which evaluated the safety, preliminary efficacy, and PK of multiple doses of GSK3195165 in subjects (N=96) with active, mild-moderate RA [Behrens, 2015]. Previous treatment with biological/immunosuppressive therapies other than cell-depleting agents was allowed with an adequate washout period. Eligible patients had active moderate RA (1987 American College of Rheumatology [ACR] RA classification criteria, ≥3 swollen and ≥3 tender joints), an elevated C-reactive protein (CRP) >5 mg/L (in sero-negative subjects) or CRP >2 mg/L (in Rheumatoid factor [RF] and/or Anti-cyclic citrullinated protein antibody [ACPA] sero-positive subjects) and Disease activity score for 28 different joints (DAS28) score ≤5.1. Subjects received 4 IV weekly doses of GSK3195165 at 0.3 mg/kg, 1.0 mg/kg or 1.5 mg/kg or placebo in addition to stable concomitant treatment with Disease modifying antirheumatic drugs (DMARDs) or low doses of oral corticosteroids. Rapid and significant reductions in disease activity (as measured by DAS28) were observed with the 1.0 mg/kg and 1.5 mg/kg doses. Greater reduction in disease activity to Week 4 was

observed with 1.0 mg/kg than 1.5 mg/kg in this dose-escalation cohort study. A significant reduction in mean DAS28 was not observed in the 0.3 mg/kg group. Other disease activity measures (e.g., ACR response) and patient-reported outcomes were consistent with the results for DAS28. GSK3196165 was generally safe and well-tolerated in this study. Treatment emergent adverse events (AEs) in the GSK3195165 groups were mild or moderate in intensity and generally reported at frequencies similar to those in the placebo group. Infections were the most commonly reported AEs and occurred in 26.1% and 29.6% of GSK3196165 and placebo subjects, respectively. There was a numerical imbalance in cough (0/27 placebo, 3/69 active). There were no apparent trends in Pulmonary function tests (PFTs) or Diffusing capacity of the lung for carbon monoxide (D_{LCO}) changes. In two cases, AEs were classified as serious because of hospitalization: paronychia in a placebo subject and pleurisy (which responded to antibiotics and therefore may have had an infectious etiology) in a GSK3195165 0.3 mg/kg subject. Both patients recovered.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To assess the efficacy potential of GSK3196165 on pain in inflammatory HOA.	• Change from baseline in 24h average hand pain intensity at Week 6, as measured by daily pain Numerical Rating Scale (NRS) averaged over the 7 days prior to assessment visit.
Secondary	
• To evaluate impact of GSK3196165 on average and worst HOA pain, over time.	• Change from baseline in 24h average hand pain intensity at each visit, measured by daily pain NRS and averaged over the 7 days prior to each assessment visit. • Change from baseline of worst hand pain intensity over 24h at each visit, measured by daily NRS and averaged over the 7 days prior to each assessment visit. • Proportion of subjects in each treatment group achieving a 30% reduction in 24h average hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit. • Proportion of subjects in each treatment group achieving a 50% reduction in 24h average hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit. • Proportion of subjects in each treatment group achieving a 30% reduction in 24h worst hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit.

Objectives	Endpoints
	• Proportion of subjects in each treatment group achieving a 50% reduction in 24h worst hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit.
• To assess the impact of GSK3196165 on hand pain (on use), stiffness and function, over time.	• Change from baseline in Australian Canadian Hand Osteoarthritis Index (AUSCAN) 3.1 NRS, total and domains (pain, morning stiffness, function) scores at each visit.
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• To assess potential impact of GSK3196165 on disease activity in HOA,	• Change from baseline in patient global assessment (PtGA) and physician global assessment (PhGA) of disease activity at Week 6,12 and 22.
• To assess safety of GSK3196165 in HOA patients, over the study duration.	• Incidence of adverse events and serious adverse events. • Incidence of infections. • Incidence of pulmonary events (cough/dyspnea, PAP and D_{LCO}). • Immunogenicity.
• To assess population pharmacokinetics of GSK3196165 in HOA.	• Population pharmacokinetics endpoints such as CL/F, Vss/F, Ka.
Exploratory	
• To explore the potential impact of GSK3196165 on disease progression/modification in HOA, using MRI imaging.	• Change from baseline in synovitis in the affected hand*, as measured by DCE-MRI including the exchange rate (K^{trans}), interstitial volume (v_e), plasma volume (v_p), volume of synovitis, initial rate of enhancement (IRE), and maximum signal intensity enhancement (ME). • Change from baseline in structural and inflammatory HOA features in the affected hand* (including synovitis, erosive damage, cysts, osteophytes, cartilage space loss, malalignment, and bone marrow lesions) as assessed by the OMERACT HOAMRIS scoring system • Change from baseline in structural and inflammatory HOA features in the affected hand* (including synovitis, bone erosions, joint space width, and bone marrow edema) as assessed by the RAMRIQ scoring system. • Change from baseline in bone shape as assessed by structural MRI of the affected hand*.
• The exploration of the relationship	• Relationship between concentration or PK

Objectives	Endpoints
between GSK3196165 PK and PD effects and/or efficacy.	parameters and PD endpoint(s).
• To evaluate the potential of GSK3196165 to affect biomarkers of HOA.	• Change in blood biomarkers from baseline at each visit.

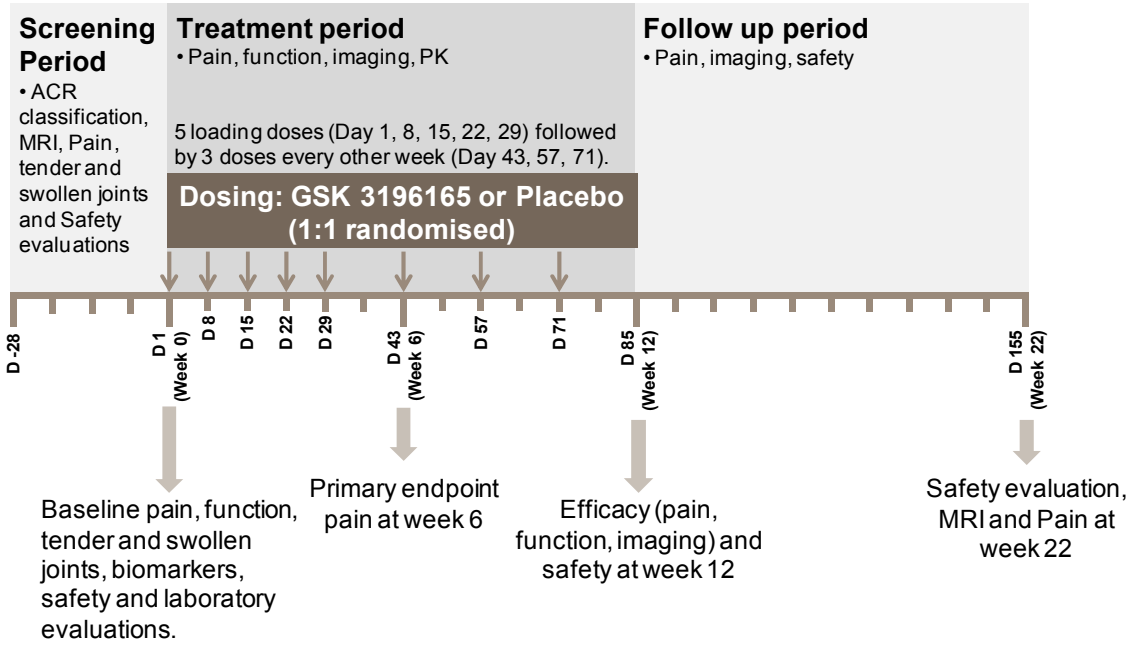
* If only one hand is affected by HOA and meets the inclusion criteria, the affected hand will be documented at screening and used for all assessments. In cases where both hands are affected by HOA and both meet the inclusion criteria, then the dominant hand will be documented at screening and this hand will be used for the MRI assessments throughout the study.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized Phase IIa, multicentre, double-blind, placebo-controlled parallel group study with the primary objective to assess the efficacy potential of GSK3196165 on pain, in subjects with active inflammatory HOA.

4.2. Study Schematic



Approximately 40 subjects will be enrolled into the study, following a screening period of up to 4 weeks. The total treatment period will be 12 weeks, with the follow up period completing at Week 22. At least 40 subjects will be randomized across the two treatment arms, to either placebo or GSK3196165 in a 1:1 ratio (n=20 per arm).

- This study will be double-blind (sponsor unblind). Refer to Section 6.4 for details of blinding.

- For screening, baseline and efficacy assessments, the average pain intensity over 7 days prior to assessment date will be used. This is calculated from collected daily pain NRS data over 7 days.
- Imaging MRI will be carried out at screening, Week 12 and Week 22. (Note: MRI at screening will serve as the baseline measurement).
- At baseline subjects will be evaluated by pain NRS (average 7 days prior to visit), AUSCAN 3.1 NRS, PtGA, PhGA, number of tender and swollen joints in their hands and blood will be collected for safety, biomarker monitoring, and pharmacokinetics.
- Throughout the study treatment period, subjects will be assessed for hand pain using a daily pain NRS questionnaire (daily from screening to Week 12). In addition, at the specified time points (see Section 7.1, time and events table), function and disease state will be assessed using the AUSCAN 3.1 NRS, PtGA and PhGA. The number of tender and swollen joints in affected hands will also be assessed and blood samples will be collected for safety, biomarkers monitoring, and pharmacokinetics.
- At the Week 22 follow up visit, blood will again be collected for safety monitoring as well an assessment of pain NRS (average 7 days prior to visit), PtGA, PhGA and MRI imaging of the affected hand.

For MRI endpoints the assessments are based on one hand only. In cases where both hands are affected by HOA and both meet the inclusion criteria, then the dominant hand will be documented at screening and this hand will be used for the MRI assessments throughout the study.

4.2.1. Pharmacokinetics

The study will use sparse sampling of GSK3196165 to determine PK parameters and associated inter- and intra-subject variability. The relationship between GSK3196165 concentrations and PD effects and/or efficacy endpoints will be evaluated if appropriate, as an exploratory endpoint.

4.2.2. Biomarkers

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

4.3. Treatment Arms and Duration

- A screening period of up to 4 weeks, will be followed by a 12 week treatment period (dosing with GSK3196165 or placebo) then a follow up period, completing on week 22. The total study duration for an individual subject will be approximately 26 weeks.

- The Study consists of 2 arms: treatment with GSK3196165 or placebo will be given as a single subcutaneous injection (shielded to subjects) to the abdomen or thigh, by an unblinded administrator weekly for 5 injections, from Week 0 to Week 4 (Days 1, 8, 15, 22, 29), then every other week for 3 further injections, from Week 6 until Week 10 (Days 43, 57 and 71).
- In total, each subject will receive up to 8 doses of study treatment.

4.4. Type and Number of Subjects

Approximately 40 subjects with active inflammatory HOA who have passed all screening assessments, will be enrolled onto the study. At least 40 subjects will be randomized across the two treatment arms, to either placebo or GSK3196165, in a 1:1 ratio (n=20 per arm).

4.5. Design Justification

This study is designed to investigate whether GSK3196165 may be a treatment option for inflammatory HOA.

The primary objective is to demonstrate a reduction in pain at week 6, as indicated by an improvement of at least 2 points in 24h average pain score measured by pain NRS (0-10) for active vs. placebo, which is considered a clinically important difference [Farrar, 2008; Salaffi, 2004 and Farrar, 2001]. In order to minimise effect of daily fluctuations in patients' perception of pain, baseline and efficacy assessments will use a 7 day average of the 24h average pain NRS. Considering the mechanism of action for anti-GM-CSF and results from earlier trials in RA it is likely that an impact on pain would be seen within the 6 week timeframe.

Secondary endpoints include evaluation of 24h average pain NRS, 24h worse pain NRS and responder analysis. In addition, hand function, pain on use and stiffness which will be assessed by AUSCAN Hand Osteoarthritis Index 3.1 NRS. The AUSCAN Index is a self-administered questionnaire that assesses the three dimensions of pain on use, function and joint stiffness in hand osteoarthritis using a battery of 15 questions with 11-point (0-10) NRS response options and a 48-hour recall period. The AUSCAN is a valid, reliable and responsive measure of outcome and we have chosen the NRS format of the AUSCAN in order to provide consistency and ease of use for the patient [Kloppenburg, 2015; Poole, 2011 and Bellamy, 2002].

Additionally, exploratory MRI imaging (including Dynamic Contrast Enhanced Magnetic Resonance Imaging [DCE-MRI], structural bone shape, the Outcome Measures in Rheumatology Hand Osteoarthritis Magnetic Resonance Imaging Scoring System (OMERACT HOAMRIS) [Haugen, 2014], and the Rheumatoid Arthritis Magnetic Resonance Imaging Quantitative Score (RAMRIQ) system [Bowes, 2014]) will be employed to explore a potential effect of GSK3196165 on disease modification, which includes a reduction in inflammation in terms of synovitis and bone marrow lesions, and structural progression in terms of cartilage space loss (as an analog of joint space narrowing) and bone shape.

All study endpoints will be evaluated at week 12, following the completion of dosing, to assess the effect of GSK3196165 on hand function and disease modification, given it is unclear how soon these effects could be seen due to the minimal amount of historic data in HOA. A follow up (observational) period, will then take place, completing the study at Week 22.

The purpose of this study is to provide an initial assessment of the therapeutic potential in this indication. Therefore, it is considered appropriate to study the highest dose possible (within safety margins), so as not to miss potential efficacy within this exploratory study. Placebo is the most relevant control given the small size of this study and that drugs are not considered to be very effective in this disease state (Non-steroidal anti-inflammatory drug [NSAIDs] non-responder) [Gelber, 2015; Chevalier, 2014; Bijlsma, 2011; Altman, 2010 and Towheed, 2005]. Secondly standard of care is variable across different countries and hence picking one relevant comparator is very challenging. Further given the subjective nature of measuring pain response it is important to run this study in a double blinded fashion.

4.6. Dose Justification

The recommended dosing regimen for this study includes five loading doses of 180 mg SC administered every week, followed by maintenance doses of 180 mg SC administered every other week. The predicted PK plasma profile of GSK3196165 at this dose is shown in Figure 1 below. This regimen was selected i) to produce sufficient drug exposure in both plasma and synovial fluid to inhibit free GM-CSF and ii) to be associated with a appropriate margin to the No Observed Adverse Effect Level (NOAEL) and the No Effect Level (NOEL) (the dose at which foamy alveolar macrophages were not observed in the 13-week rhesus monkey study). Further details are provided below.

- The C_{min} steady-state plasma levels at this dose are predicted to be equal or greater than 2 µg/mL, which is the hypothetical plasma concentration required to bind synovial GM-CSF based on in vitro data. Similarly, a mechanistic model, based on Pharmacokinetics (PK) characteristics of a typical IgG1 [Choy, 2000; Cao, 2013 and Pejovic, 1995] and GM-CSF binding [Bell, 1995] predicted at least 90% inhibition of free GM-CSF in both plasma and synovial fluid.
- The mean steady-state plasma levels predicted at this dose would allow a 26-fold margin to the NOAEL (50 mg/kg), where reversible minimal to mild foamy alveolar macrophages (considered non-adverse) were seen in the 26-week monkey toxicity study, with a 14-and 3-fold margin to the NOEL dose levels (30 and 5 mg/kg) identified in the 13 and 26 week monkey toxicity studies (see Table 1 below).

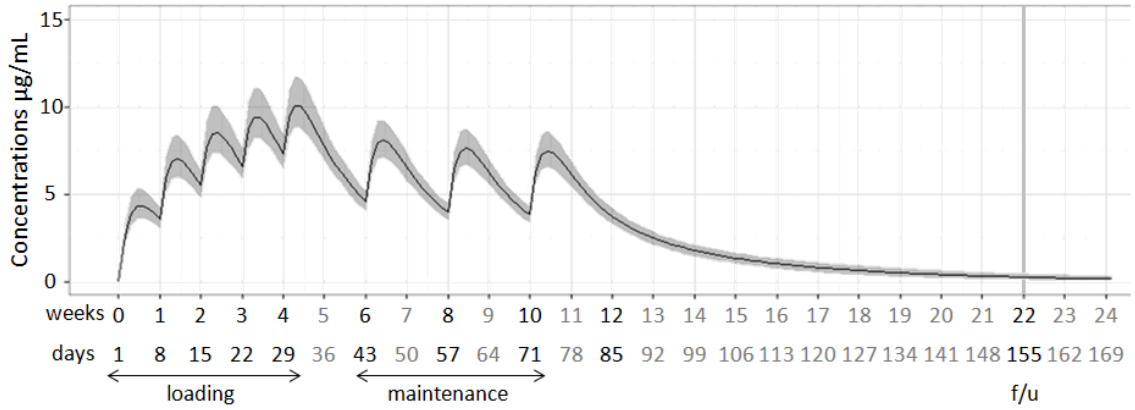
Table 1 Safety margins with 180 mg SC GSK3196165 relative to exposures in nonclinical toxicology studies

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

IV intravenous; SC subcutaneous

a. Simulated mean AUC based on analysis of SC and IV data for doses ≥0.5 mg/kg from study MSC1000 (N=18) and study MOR103C104 (N=32) with a 2 compartment model and calculation of F by ratio of Cl_{IV}/Cl_{SC} with bioavailability of 44% (95% CI 37%-53%)
b. As there were no significant differences on sampling occasions or gender differences within each primate study, the end of study mean AUC (0-168) values have been used and multiplied by 2 to obtain mean concentrations over a two week period
c. No observed adverse effect dose level (NOAEL)
d. No observed effect dose level (NOEL)

Figure 1 Predicted GSK3196165 plasma concentrations at the recommended dosing regimen (median and 95% confidence interval)



4.7. Benefit:Risk Assessment

Since GSK3196165 is still in early development with limited efficacy and safety data available, an integrated Benefit/Risk evaluation has not been performed at this point in time. Summaries of findings from both clinical and non-clinical studies conducted with GSK3196165 can be found in the IB and IB supplement [GSK Document Number 2014N190256_00 and GSK Document Number 2015N226819_00]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.7.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3196165		
Infections	Immune-modulating biologic drugs (such as anti-Tumor necrosis factor [TNF] agents) are associated with an increased risk of serious and opportunistic infections. Similarly, because of the role of GM-CSF in anti-infective immunity, GSK3196165 also has the potential to increase the risk of infection. **Non-clinical Data:** No changes in peripheral blood populations (lymphocytes, neutrophils, monocytes, eosinophils or basophils), phagocytic activity of peripheral blood polymorphonuclear cells (investigational endpoint in the 26 week study), T-cell dependent response, B-cell primary or secondary response, or circulating cytokine levels (26 week study) were observed. Studies in knock-out mice showed that GM-CSF deficiency (GM-CSF-/-) affects the ability of mice to control infection when infected with *M. tuberculosis* or pulmonary group B *streptococcus* [LeVine, 1999]. **Clinical Data:** One healthy volunteer in study MSC-1000 experienced septic shock secondary to pneumonia 29 days after receiving a single dose of IP at 1.5 mg/kg. Subject recovered after treatment with antibiotics, and the subject completed the study follow-up period as per protocol. One RA subject in study MSC-1001 experienced serious pleurisy which responded to antibiotics.	**Subject selection :** • Subjects with active infections or a history of recent or recurrent infections are not permitted to enter the study. • Subjects with significant leukopenia (white blood cell count ≤3.0 x10^9/L) and neutropenia (absolute neutrophil count ≤1.5 x 10^9/L) are not permitted to enter the study. • Subjects will be screened for TB, HIV and Hepatitis B and C, and excluded from study participation if positive. Subjects with any past history of TB or Hepatitis B will also be excluded. • Investigators are expected to assess vaccination status, including against influenza and pneumococcus, according to local guidelines. **Subject monitoring:** • Serious infections are categorised as adverse events of special interest (AESIs). • Subjects will be closely monitored for infections and additional information to clarify the events will be recorded in the eCRF. Appropriate diagnostic tests will be considered during the study if clinically indicated to ensure appropriate safety monitoring. • Subjects will be instructed as to the signs and symptoms of infection, and to contact site personnel should they develop. This information will also be contained within the patient Informed Consent Form. **Withdrawal criteria:** • In the event of a serious infection, study medication should be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		discontinued and the subject withdrawn from the study.
Pulmonary alveolar proteinosis (PAP)	GM-CSF signalling is required to maintain the normal function of alveolar macrophages. Long-term absence of GM-CSF signalling (*e.g.*, via hereditary GM-CSF deficiency or development of anti-GM-CSF auto-antibodies) is known to cause the extremely rare condition of PAP, which is characterized by the accumulation of surfactant lipids and protein in the alveolar spaces, with resultant impairment in gas exchange. **Non-clinical Data:** Non-adverse minimal to mild foamy alveolar macrophage accumulation were noted in lungs of monkeys in the 13-week SC and 26-week IV toxicology studies, but reversible following off drug period. Dose levels at which foamy alveolar macrophages were not observed were identified in these studies. **Clinical Data:** No cases of PAP have been reported to date in the clinical development program. Furthermore evaluation of pulmonary function has not demonstrated any abnormalities in pulmonary functions.	**Subject selection** • Subjects with history of clinically-significant respiratory diseases that required treatment and/or follow up, or chronic cough or dyspnea will not be permitted to enter the study. • Pulmonary function testing (spirometry, D_{LCO}) will be performed at baseline in order to exclude those subjects with impairment. Subjects with abnormal D_{LCO} or Forced expiratory volume in one second (FEV1) will be excluded. **Dose Duration:** • The exposure duration to GSK3196165 in this study is 3 months. Although the time course of Pulmonary alveolar proteinosis (PAP) development in humans is unknown, the published literature suggests that it requires full inhibition of GM-CSF for years before clinical manifestation of the disease can be detected (refer to IB GSK Document Number 2014N190256_00 for further details). Therefore, the risk of development of PAP in this study is anticipated to be low. **Subject Monitoring:** • Specific pulmonary assessments are a requirement of the study protocol: ○ Subjects will be assessed every visit for the development of cough and dyspnea, and will also have regular chest auscultation and pulse oximetry measurements. Persistent cough or dyspnea will be reported as an AESI. ○ Pulmonary function testing (spirometry and D_{LCO} measurements) will be performed at baseline, and then at week 12 and at the follow-up visit. Relative change in D_{LCO} >15% from baseline will be reported

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		as an AESI if confirmed with three consecutive weekly tests. • In the event of any new or clinically significant pulmonary abnormalities that may develop during the study and persist for three consecutive weeks (e.g., increased shortness of breath/dyspnea, or unexplained and persistent coughing; or >15% relative decrease in D_{LCO} from baseline), the subject will be withdrawn from study drug for the remainder of the study and it is recommended that the subject be referred to a pulmonologist for further assessment [Section 5.5.1]. The subject should be followed until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined. Suggested pulmonary assessment and management algorithms are provided in Appendix 6.
Hypersensitivity reactions, including anaphylaxis	There is a potential risk of hypersensitivity reactions, including anaphylaxis, during and following the administration of protein-based products, such as GSK3196165. **Clinical Data**: No allergic or acute systemic reactions have been observed to date in the clinical development program.	**Subject selection** • Subjects with a history of sensitivity to any of the study treatments, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation, will not be permitted to enter the study. **Study treatment administration/Subject monitoring:** • All SC administrations will be performed at the clinical site. • Subjects will be required to remain monitored at the site for 1 hour after the injection for the first 3 injections, and then for 30 minutes for subsequent injections. • Subjects should be informed of the signs and symptoms of an acute hypersensitivity reaction, and be instructed to seek immediate medical care should they develop. This information will also be contained within the patient Informed Consent

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Form. • Should hypersensitivity or anaphylaxis occur, subjects should be managed appropriately per local guidelines/medical judgement. • Severe or serious hypersensitivity or anaphylaxis are categorised as AESIs. **Subject monitoring:** • Subjects should be monitored for hypersensitivity reactions throughout the study, and the information recorded in the eCRF. • Any clinically-significant event should be reported as an AE. **Withdrawal criteria:** • In the event of severe or serious hypersensitivity or anaphylaxis, study medication should be discontinued and the subject withdrawn from the study.
Injection site reactions	SC injections may be associated with local reactions (*e.g.*, swelling, induration, pain). **Non-clinical & Clinical Data:** No macroscopic or microscopic changes indicative of local injection site reactions were observed following IV or SC administration.	**Subject monitoring:** • Subjects should be monitored for injection site reactions throughout the study, and the information recorded in the eCRF. • Injection sites will be rotated. • Any clinically-significant event should be reported as an AE.
Immunogenicity	**Pre-clinical Data** Anti-drug antibodies (ADAs) to GSK3196165 were detected in some monkeys and was associated with reduced serum levels of GSK3196165; ADA associated toxicity was not observed. **Clinical Data** In Study MSC1000, one healthy volunteer who received a single dose of 25 µg/kg developed an IgM ADA at Day 15, and in Study	**Investigate Risk** • Samples (pre-and post-baseline) will be collected from all subjects during the study to assess development of anti drug antibodies and will be analyzed at the end of the study. • In addition to scheduled immunogenicity assessments, "event-driven" testing will also be employed for those subjects that experience anaphylaxis, serious

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	MSC1001 one RA subject who received 4 weekly doses of 1.0 mg/kg dose developed an IgG ADA at Week 13, but not at Week 16 (with no impact on GSK3196165 serum concentration).	hypersensitivity or adverse events that are deemed to be clinically significant in the opinion of the investigator, and related to study drug administration that lead to withdrawal from the study, blood samples will be taken for immunogenicity testing at the time of the event and again 12 weeks after.
Neutropenia	Although there is a perceived theoretical risk that GM-CSF blockade may affect maturation of leukocytes and their precursors, mice lacking GM-CSF do not develop neutropenia or show any major perturbation of hematopoiesis [Stanley, 1994]. **Non-clinical & Clinical Data:** There have been no reports of neutropenia or decreases in leukocytes in the non-clinical and clinical GSK3196165 program.	**Subject selection** • Subjects with significant leukopenia (WBC ≤3.0 x 10^9/L); thrombocytopenia (platelet count ≤100 x 10^9/L); neutropenia (absolute neutrophil count ≤1.5 x 10^9/L); lymphocytopenia (≤0.8 x 10^9/L) within 28 days prior to Day 1 are not permitted to enter the study. **Subject monitoring:** • A full blood count (with differential) will be performed at regular intervals throughout the study (ref. Time and Events Table,). • Grade 3 or 4 neutropenia will be reported as an AESI.
Reproductive toxicity	Published studies performed with GM-CSF -/- mice have indicated that GM-CSF depletion potentially affects fertility, establishment of pregnancy and post partum development of offspring in the mouse. **Non-clinical Data:** No GSK3196165-related effects on female or male fertility were noted in the SC 13-week repeat dose monkey study at doses up to 100 mg/kg/week (highest dose tested). In addition no maternal, embryofoetal or effects on fertility were noted in the reproductive toxicology studies using the surrogate rat anti-mouse GM-CSF monoclonal antibody, 22E9. The effect on human pregnancy is unknown.	**Subject selection** • Male and female subjects will only be permitted to enter the study if they meet the contraception requirements detailed in inclusion criterion • In addition, females of child bearing potential will undergo pregnancy testing at screening and at regular intervals during the study (ref. Time and Events Table, Section 7.1). **Withdrawal criteria:** • In the event of a pregnancy in a female subject in the study, study medication should be discontinued and the subject withdrawn from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical Data: No HVs or RA subjects became pregnant during the studies, but one MS subject was found to be pregnant during study MOR103C10301028 and received four 2.0 mg/kg doses, the pregnancy was terminated 2 weeks later by elective abortion.	**Other considerations** • Female subjects who become pregnant will be followed to determine the outcome of the pregnancy. If a female partner of a male subject becomes pregnant, they will be followed to determine the outcome of the pregnancy. • Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Malignancy	Immunomodulatory therapies may increase the risk of malignancy. **Non-clinical & Clinical Data:** There have been no reports of malignancy in the non-clinical and clinical GSK3196165 program.	**Subject selection** • 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.
Study Procedures		
Exposure to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner.	**Subject Selection:** All participants will be screened according to local hospital criteria and trial inclusion/exclusion before entering the MRI room to ensure they are able to have the MRI conducted. Subjects with non-MR compatible metal implants or implantable electronic devices (e.g. pacemaker, defibrillator) will not be included in this study.
Gadolinium (Gd) containing MRI contrast agents	**Non-clinical data:** Animal studies have shown reproductive toxicity of gadolinium-containing MRI contrast agents at repeated high doses. **Clinical data:** Use of MRI contrast agents in subjects with severely impaired renal	**Subject Selection:** • Pregnant or breast feeding females will be excluded from taking part in the study. • Subjects with impaired renal function (GFR<60ml/minute) are excluded by the eligibility criteria. • Subjects with history of sensitivity to Gd-containing contrast agents will be excluded from the study. The MRI procedure will

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	function (Glomerular filtration rate [GFR]<30ml/minute) has been associated with Nephrogenic Systemic Fibrosis (NSF). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed against the risks. Gd contrast agents can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock. In general, subjects with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions. The risk of hypersensitivity reactions may be higher in case of: • previous reaction to contrast media • history of bronchial asthma • history of allergic disorders Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely observed.	be conducted under the supervision of a trained and qualified clinical staff who are trained to appropriately manage an allergic reaction. • Sites will be responsible for following any additional safety information for the specific gadolinium contrast agent used at their site and not enrol subjects if contraindicated. **<u>Subject monitoring and management:</u>** • MRI contrast at a dose less than or equal to 0.1 mmol/kg will be used in the MRI protocol. Effective contraception is required during the study, and pregnancy tests will be performed regularly throughout the study prior to dosing in females of child bearing potential.

4.7.2. Benefit Assessment

Pain associated with HOA does not respond well to current analgesic treatments [Gelber, 2015; Chevalier, 2014; Bijlsma, 2011; Altman, 2010 and Towheed, 2005]. Thus subjects entering the study, who receive active drug, have the potential to receive benefit over 12 weeks of treatment.

Participation in this study will contribute to the evaluation of a potential new therapy in an area of high unmet need.

4.7.3. Overall Benefit:Risk Conclusion

GSK3196165 is a high-affinity recombinant monoclonal antibody (mAb), IgG1 lambda, that binds specifically to human GM-CSF and neutralises its biological function resulting in an anti-inflammatory and anti-nociceptive effect in addition to affecting bone metabolism through the RANKL pathway and may therefore be a viable treatment option in osteoarthritis

Key potential risks are those described above that may be associated with inhibition of GM-CSF (*e.g*., pulmonary toxicity, infection) and those associated with administration of a therapeutic monoclonal antibody (*e.g*. allergic reactions). Robust and systematic safety monitoring will be undertaken in studies of GSK3196165 to proactively address and mitigate the potential risks.

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 HOA.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GSK Document Number 2014N190256_00] and IB supplement [GSK Document Number 2015N226819_00].

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

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Meets ACR classification of OA and is intolerant to, or has not responded to analgesics (level 1 and 2) or to NSAIDs for at least 10 days in the past 3 months.
3. Must have active disease with **at least two swollen and tender PIP and/or DIP joints** in the affected hand*.
4. Signs of inflammation such as synovitis in the MRI scan of the affected hand*.
5. Must have a patient's self assessment of 24h average hand pain intensity of at least '5' on an 11-point NRS (0-10), calculated as an average using data from the 7 days prior to assessment date.

*If only one hand is affected by HOA and meets the inclusion criteria, the affected hand will be documented at screening and used for all assessments. In cases where both hands are affected by HOA and both meet the inclusion criteria, then the dominant hand will be documented at screening and this hand will be used for the MRI assessments throughout the study.

WEIGHT
6. Body weight ≥ 45 kg.

SEX
7. Male or female subjects are eligible to participate so long as they meet and agree to abide by the contraceptive criteria detailed in Appendix 5.

INFORMED CONSENT
8. Written informed consent prior to any of the screening procedures including discontinuation of prohibited medications.

OTHER SAFETY-RELATED
9. Diffusing capacity of the lung for carbon monoxide (DLCO) ≥ 70 % predicted and forced expiratory volume in 1 second (FEV1) ≥ 80 % predicted.
10. No evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following:
a. No history of active or latent TB infection irrespective of treatment status.

b. A negative diagnostic TB test within 28 days of baseline (Day 1) defined as: a negative QuantiFERON Gold test or T-spot test (may be performed locally) (NB: 2 successive indeterminate QuantiFERON tests will be considered as a positive result).

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

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

1. Pregnant or lactating females.
2. Significant unstable or uncontrolled acute or chronic disease (*e.g.*, cardiovascular including uncompensated congestive cardiac failure NYHA III or IV, myocardial infarction within 12 months, unstable angina pectoris, uncontrolled hypertension, hypercholesterolemia) pulmonary, hematologic, gastrointestinal (including Crohn's Disease or ulcerative colitis), hepatic, renal, neurological, psychiatric, malignancy, endocrinological, immunologic or infectious diseases, which, in the opinion of the investigator, could confound the results of the study or put the subject at undue risk.
3. History of any clinically significant inflammatory disease other than inflammatory HOA, especially, but not limited to, rheumatoid arthritis or spondylarthropathies.
4. Diagnosis of rheumatoid arthritis, fibromyalgia, gout, calcium pyrophosphate deposition disease CPPD, pseudogout, hemochromatosis or other inflammatory rheumatological or autoimmune disorders.
5. Clinical suspicion of, or previous investigation for CPPD or pseudogout, or history of chondrocalcinosis.
6. Any injury, medical or surgical procedure to the affected joint(s) that may interfere with evaluation of the target HOA joint(s).
7. History of any clinically-significant respiratory disease that required treatment and/or follow up under the direction of a physician or any respiratory disease which in the opinion of the Investigator would compromise the ability of the subject to complete the study (*e.g*. interstitial lung disease, such as pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], moderate-severe asthma, bronchiectasis, pneumonitis, pulmonary alveolar proteinosis (PAP), significant exposure to pneumotoxins (*e.g*. inhaled silica).
8. Clinically-significant or unstable (in the opinion of the Investigator) persistent cough or dyspnea that is unexplained.
9. QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block based on averaged values of triplicate electrocardiograms obtained over a brief (e.g. 5-10 minute) recording period
   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or

manually over-read.

10. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
11. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
12. 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.
13. Kidney disease**:** Current or history of renal disease, or estimated creatinine clearance <60 mL/min/1.73m^2 or serum creatinine >1.5xULN within 28 days of Day 1.
14. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
15. 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.
16. Active infections, or history of recurrent infections (excluding recurrent fungal infections of the nail bed), or have required management of acute or chronic infections, as follows:
    a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).

    OR

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

    OR

    c. Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 26 weeks of Day 1 or oral antimicrobials within 14 days of Day 1.

17. A vaccination (live or attenuated) within 30 days of Day 1 or BCG vaccination within 365 days of Day 1, or a live vaccination planned during the course of the study.
18. Any surgical procedure, including bone or joint surgery/synovectomy within 12 weeks prior to Day 1 or any planned surgery within the duration of the study or follow-up period.
19. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but not limited to:
    a. Intracranial aneurysm clips (except Sugita) or other metallic objects,
    b. History of intra-orbital metal fragments that have not been removed by an medical professional,
    c. Pacemakers or other implanted cardiac rhythm management devices and non-MR compatible heart valves,
    d. Inner ear implants, except MR-conditional implants scanned within manufacturer guidelines,
    e. History of claustrophobia which may impact participation

CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES
20. Use any of prohibited medications, as listed in Section 6.10.2, throughout the study until after completion of the week 22 follow-up visit. Prohibited medications must be discontinued for the stated time in Section 6.10.2 prior to Day 1. Note: For patients who need to discontinue prohibited medication > 28 days prior to Day 1, written informed consent for the study must be obtained prior to this discontinuation, however screening assessments other than consent must still occur within the 28 days prior to Day 1.

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

CONTRAINDICATIONS
22. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation. 23. Contraindication to gadolinium contrast agent as assessed by the site.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
24. Must have negative titer rheumatoid factor (RF) and anti-CCP antibody. 25. Any Grade 3 or 4 hematology or clinical chemistry laboratory abnormality [CTCAE, 2009 v4.0] within 28 days of Day 1. 26. Hemoglobin ≤9 g/dL; white blood cell count ≤3.0 x10^9/L; platelet count ≤100 X 10^9/L; absolute neutrophil count ≤1.5 x 10^9/L; lymphocyte count ≤0.8 x 10^9/L within 28 days of Day 1. 27. Presence of hepatitis B surface antigen (HBsAg) and/or presence of hepatitis B core antibody (HBcAb) at screening. 28. Positive hepatitis C antibody test result at screening. Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA PCR test is obtained. 29. Positive serology for human immunodeficiency virus (HIV) 1 or 2 (within 28 days of Day 1). 30. A positive pre-study drug/alcohol screen. 31. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 32. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.5).

5.3.1. Re-Screening

If a subject has not met all the eligibility criteria within the 28 day screening period, re-screening is required. Subjects are only allowed to be re-screened once; the entire screening process must be repeated.

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 Study Reference Manual (SRM).

5.3.2. Re-Testing – Laboratory Exclusion

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

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

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

5.4. Withdrawal/Stopping Criteria

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

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

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

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

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

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

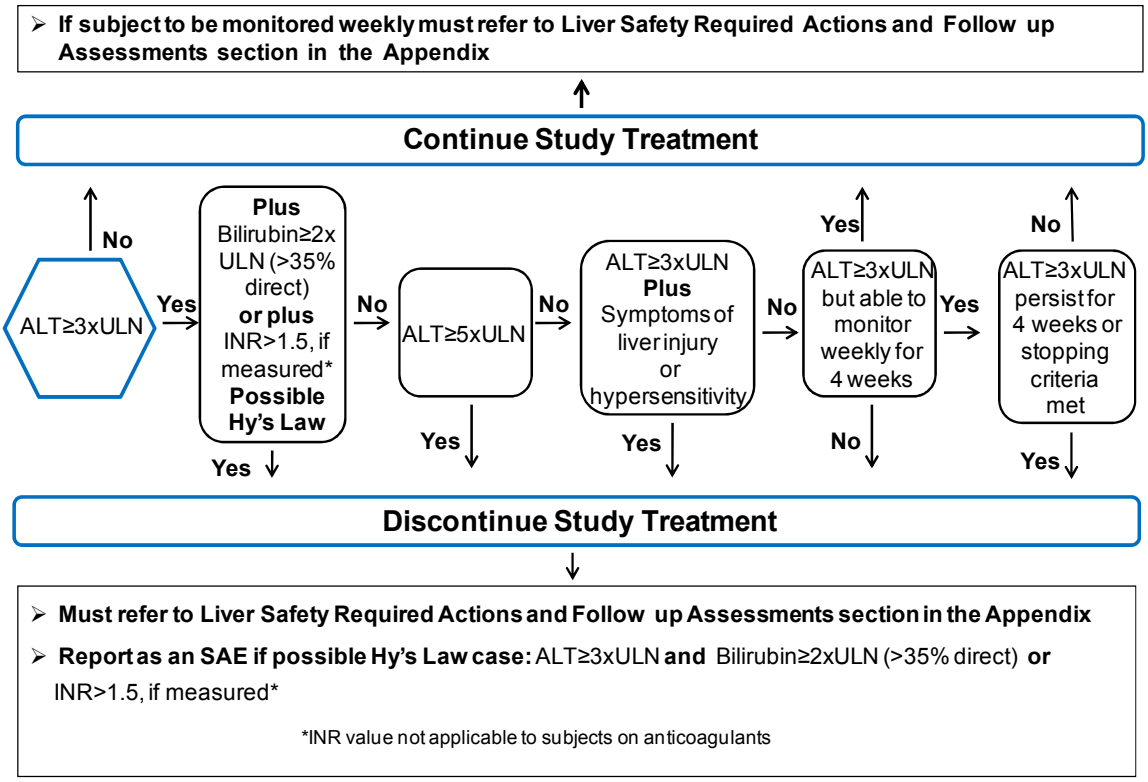
If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. In each case the reason for withdrawal will be recorded in the eCRF.

A subject that is withdrawn early from the study after being randomized to treatment cannot be re-screened, but should be encouraged to return for the Early 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.1.1. Study Treatment Restart or Rechallenge

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

5.4.2. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety Electrocardiogram (ECGs) and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g. 5-10 minute) 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 patients 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 withdrawal

Subjects will be permanently withdrawn from study treatment if any of the following respiratory symptoms or hematologic abnormalities are seen, investigation will be carried out as described below. After withdrawal of treatment under these conditions, where possible subjects should remain in the study (off treatment) in order to complete all remaining visits/assessments.

5.5.1. Respiratory Symptoms

Any of the following persistent respiratory symptoms must be reported as an AE and **require withdrawal of study medications for the remainder of the study** and further investigation as below:

- Persistent reduction in D_{LCO} >15% relative decrease from baseline for three consecutive weeks
- Persistent cough (Common terminology criteria [CTC] grade 2 or 3, see Appendix 7) for three consecutive weeks
- Persistent dyspnea (Borg CR10 scale grade 3 or above, see SRM) for three consecutive weeks.

Upon any of these persistent symptoms, it is recommended that the subject be referred to a pulmonologist for further assessment. The subject should be followed until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined. Suggested pulmonary assessment and management algorithms are provided in Appendix 6.

5.5.2. Hematologic abnormalities

The following hematological laboratory abnormalities require withdrawal of study medications *for the remainder of the study* and prompt retesting, ideally within 3-5 days:

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

Subjects should be followed as appropriate until resolution of the event. Absolute neutrophil count <1.0 x 10^9/L (Grade 3 or greater) should be reported as an AE.

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

Treatment with GSK3196165 will be given as a single subcutaneous injection to the abdomen or thigh, by an unblinded administrator (shielded to subjects).

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment	
Product name:	GSK3196165	Placebo
Function	Test (investigational product)	Control
Formulation description:	See IB [GSK Document Number 2014N190256_00] for details.	The placebo in this study will be sterile 0.9% (w/v) sodium chloride solution.
Dosage form:	Liquid	Liquid
Dosage levels (volumes):	180 mg (1.2mL)	1.2 mL
Route of Administration:	Investigational product should be administered SC into thigh or abdomen, sites should be rotated. Safety should be monitored for 1 hour after the injection, for the first 3 injections, then for 30 minutes thereafter. Such monitoring will include general safety monitoring including monitoring for systemic hypersensitivity infusion reactions and local injection site reactions. Trained rescue personnel and rescue medications/equipment must be available for use at all times.	

	Study Treatment	
Dosing instructions:	GSK3196165/placebo should be administered on the same day each week ± 1 day for the first 5 weekly doses (with a minimum of 5 days between doses, for no more than 2 consecutive doses). Following this GSK3196165/placebo should be administered on the same day every other week ± 3 days (with a minimum of 8 days between doses). GSK3196165/placebo will be discontinued as described in Section 5.4 **and** Section 5.5. Subjects will be randomized as shown in Time and Events Table, Section 7.1, and the dosing schedule should be followed as closely as possible. The unblinded administrator (study co-ordinator or nurse) assigned to the study will be required to prepare and administer the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment randomly through an Interactive Response Technology System (IRTS). Procedures must be in place to ensure the blind is maintained by any site staff involved in clinical care or assessment of the subject, and by the subject themselves. Further details are provided in the SRM. Every attempt should be made to ensure all doses are administered. If at any time the subject misses a dose, the Medical Monitor must be contacted for permission to continue study medication.	
Physical description:	Sterile, aqueous solution of purified monoclonal antibody 150 mg/mL	Sterile 0.9% (w/v) sodium chloride solution.
Method for individualizing dosage:	180 mg (1.2 mL) dose will be drawn into a small (*e.g.* 2 or 3 mL) syringe and should be dosed immediately.	A volume of 1.2 mL will be drawn into a small (*e.g.* 2 or 3 mL) syringe and should be dosed immediately.

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, prior to the start of the study, using validated internal software. Once a randomization number has been assigned to a subject, it cannot be assigned to another subject in the study, even if the original subject withdraws before taking study medication.

Randomization numbers will be assigned to subjects using an Interactive Response Technology System (IRTS). Information and telephone numbers for the IRTS will be provided in the SRM.

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

6.3. Planned Dose Adjustments

This protocol uses a fixed dose and no alteration to this dose level is allowed.

6.4. Blinding

The study will be double-blind (sponsor unblind), which means that the subject, investigator and trial staff at site (apart from unblinded administrator(s) and pharmacy staff), will be blinded to the trial treatment allocated to each individual subject. In addition, the sponsor central and local study teams will be blinded to treatment allocations, except for roles required to be 'unblind' in order to manage study conduct and oversight (including unblinded monitor(s)) and roles specified in the Reporting and Analysis Plan (RAP) as involved with the preparation and review of the planned interim analyses.

The RAP, which will be approved prior to the first unblinding, will identify the specific GSK individuals involved; outline in detail the activities of the interim analyses, and how the integrity of the study will be maintained.

At sites, there will be at least one unblinded administrator (study co-ordinator or nurse) who will prepare and administer the study treatment.

In the case of emergency unblinding (eg. through RAMOS NG or GSK Clinical support help desk), the following will apply:

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

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

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

6.5. Packaging and Labelling

The contents of the label for GSK3196165 and placebo 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 authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

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

6.8. Treatment of Study Treatment Overdose

6.8.1. Overdose of GSK3196165

There is very limited clinical safety data at this stage of development. However there have been no reports of overdose with GSK3196165 to date. The risk of overdose

occurring is considered low because GSK3196165 will be administered by an independent administrator, and the maximum volume that can be withdrawn from the vial is equivalent dose to be evaluated (1.2 mL). 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 serum sample for pharmacokinetic (PK) analysis at the time of the event, and three days after the event (unless otherwise requested by the Medical Monitor)
4. document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

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 efficacy of GSK3196165 has not yet been defined. Treatment after the end of the study will continue as per the standard of care for HOA at the site.

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 inflammation, enzymes such as Cytochrome P450 (CYP450) can be down-regulated leading to instances of reduced clearance and increased plasma concentrations of administered drugs. The administration of GSK3196165 can potentially alter circulating cytokine levels in 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, therapeutic drug monitoring should be performed in subjects being treated with drugs that are CYP450 substrates and have a narrow therapeutic index *e.g.*, warfarin or theophylline

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

The only permitted concomitant medication for the duration of this study is Paracetamol (acetaminophen) which may be taken on an as needed basis up to 4g/day or to the maximum permitted under local label.

Any use of Paracetamol (acetaminophen) will be recorded as concomitant medication. Subjects will record use of Paracetamol (acetaminophen) for hand pain on a daily basis.

Use of any other concomitant medications by subjects will be assessed during study visits.

6.10.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed below is prohibited from Day 1 (randomization) until after completion of the Week 22 follow-up visit.

In addition, these prohibited medications must also be discontinued for the stated time prior to Day 1 (randomization) as follows:

- Hydroxychloroquine must be discontinued at least 3 weeks prior to Day 1.
- NSAIDs (both systemic and topical) must be discontinued at least 22 days prior to Day 1.
- Opioid based analgesics as well as co-formulated medicines of paracetamol and opioids must be discontinued at least 22 days prior to Day 1.
- Intra-articular corticosteroids for the targeted joints in hand, hip and knee must be discontinued at least 12 weeks prior to Day 1.
- Intra-articular injection of hyaluronate for the targeted joints in hand, hip and knee must be discontinued at least 26 weeks prior to Day 1.
- Any investigational medication must be discontinued at least 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product, prior to Day 1 (whichever is longer).
- Any physical therapy (including hand splints) must be discontinued at least 28 days prior to Day 1
- "Nutraceuticals" (e.g. glucosamine and chondroitin) and alternative medicine products, unless taken at a stable dose, must be discontinued for a minimum of 12 weeks prior to Day 1.

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:

PROs must be administered prior to any other assessments being performed (at the main study site) to avoid influencing subjects. The appropriate order for the PROs and approximate time required for completion of each, should be:

Borg CR10 Scale (1 question, approx. 1-2 minutes, see SRM for details)

PtGA (1 question, approx. 1-2 minutes, see Appendix 10)

AUSCAN 3.1 NRS (15 questions, approx. 5-10 minutes, see SRM for details)

- Daily pain NRS questionnaire (2 questions, approx. 1-2 minutes, see Appendix 8 and Appendix 9) will be completed by subjects at home, starting on Day 1 of screening (although training, including an example pain NRS questionnaire, may be given during the Day 1 screening visit at the site). Patients will be instructed to complete the pain NRS questionnaire at approximately the same time each day (e.g. between 6pm-10pm).
- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-lead ECG
    2. vital signs
    3. blood draws.

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

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Tables

7.1.1. Screening period Time and Events table

Subject Screening (must be carried out ≤ 28 days prior to Day 1)		
Screening Day 1	Screening Days 1-7, at home	Screening Day ≥8
↓		↓
Informed Consent	Daily Pain NRS questionnaire[2]	Pain NRS eligibility assessment[3]
Inclusion/exclusion criteria		MRI[4]
Demographics		
Medical/medication/alcohol history		
Con. Med. Review		
Vital signs		
12-lead ECG		
Full Physical Exam		
Swollen and tender joints[1]		
Haem/Chem/Urinalysis		
HIV, TB, Hepatitis B & Hepatitis C screen		
RF, ACPA (anti-CCP)		
Pregnancy test (serum)		
Urine drug / alcohol screen		
Spirometry (FEV1, FVC) & D_{LCO}		
Pain NRS training		
SAE assessment		

Screening T&E table notes
1) Where possible, the same individual should perform all disease assessments for an individual subject (with separate joint assessor).
2) Pain NRS questions should be completed at approximately the same time each day (recommended between 6pm and 10pm).
3) Eligibility assessment will be based on a 7 day average of the '24h average Pain NRS' question.
4) Subjects must have passed all screening assessments, including laboratory tests and 7-day pain NRS assessment, prior to undertaking MRI scanning.

7.1.2. Treatment period Time and Events table

Study events	Screening (≤28 days prior to Day 1)	Treatment period: Week 0 Baseline & Day 1 treatment visit	Week 0 Day 3 (± 1d) PK biomarker visit	Wk 1 Day 8 (± 1d) treatment visit	Wk 2 Day 15 (± 1d) treatment visit	Wk 3 Day 22 (± 1d) treatment visit	Wk 4 Day 29 (± 1d) treatment visit	Wk 6 Day 43 (± 3d) treatment visit	Wk 8 Day 57 (± 3d) treatment visit	Wk 10 Day 71 (± 3d) treatment visit	Wk 12 Day 85 (± 3d) treatment visit	Week 20 phone call (Day 141 ± 5d)	Follow up (Week 22 (Day 155 ± 7d)
Borg CR10 Scale[1]	See separate T&E table for screening procedures	X		X	X	X	X	X	X	X	X	Site to contact subject by phone and remind them to begin completing the daily Pain NRS questionnaire starting 7 days before their Follow-up visit at Week 22	See separate table for follow-up visit procedures
Patient[1] and physician global assessment[2]		X			X		X		X		X		
AUSCAN 3.1 NRS[1]		X		X	X		X	X	X	X	X		
Brief Physical Exam		X			X		X		X		X		
Vital signs		X			X		X		X		X		
12-lead ECG		X[4]									X		
Swollen and tender joints[2]		X		X	X		X	X	X	X	X		
MRI[3]											X[3]		
Haem/Chem/Urinalysis		X		X	X		X	X	X	X	X		
PK sampling[4]		X	X	X			X	X			X		
Blood Biomarkers[4]		X	X	X	X		X		X		X		
Urine drug/alcohol		X									X		
Study treatment dosing		X		X	X	X	X	X	X	X			
Cough, Auscultation, Pulse Oximetry		X		X	X	X	X	X	X	X	X		
Spirometry (FEV1, FVC) & D_{LCO}		X									X		
Immunogenicity blood sampling		X[5]			X		X				X		
Pharmacogenetics[6]		X											
Pregnancy test (urine)		X					X		X		X		
Post-treatment Interview											X		
Daily Pain NRS questions[7]		<---------- X ---------->											
SAE/AE assessment		<---------- X ---------->											
Con. medication review		<---------- X ---------->											

Treatment period T&E table notes

1) Perform PROs before any other assessments, or procedures, to avoid influencing subject.

2) Where possible, the same individual should perform all disease assessments for an individual subject (with separate joint assessor).

3) MRI scanning at week 12 may take place on a separate day from other assessments and may occur on Day 85 (± 5d).

4) Before dosing (on dosing days).

5) Day 1 immunogenicity sample includes anti-GM-CSF auto-antibody analysis

6) Consenting subjects only.

7) Pain NRS questions should be completed at approximately the same time each day (recommended between 6pm and 10pm).

7.1.3. Follow-up visit and early withdrawal* procedures list

Subject Follow-up Visit Task List **Week 22** (Day 155 ± 7d) ↓
Borg CR10 Scale[1]
Patient[1] and physician global assessment[3]
Pain NRS assessment[2]
Vital signs
Full Physical Exam
Swollen and tender joints[3]
SAE/AE assessment
Con. Med. Review
Pregnancy test (urine)
Haem/Chem/Urinalysis
Immunogenicity
MRI[4]
PK Sampling
Blood Biomarkers
Cough, Auscultation, Pulse Oximetry
Spirometry (FEV1, FVC) & D_{LCO}

Follow-up T&E table notes
1) Perform PROs before any other assessments, or procedures, to avoid influencing subject. 2) Assessment will be based on a 7 day average of the Pain NRS questions. 3) Where possible, the same individual should perform all disease assessments for an individual subject (with separate joint assessor). 4) If scheduling MRI on the same day as the follow up visit is not possible, the MRI visit may take place on a separate day *before the Follow-up visit* but it must occur within the same Day 155 ±7day window.

*for early withdrawal, follow Day 85 procedures, then schedule a follow up visit.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.

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.

Starting at Screening Day 1, subjects will complete the daily pain NRS questionnaire (2 questions, approx. 1-2 minutes, see Appendix 8 and Appendix 9), for at least 7 days to determine their eligibility to participate in the study. Subjects will complete their first and all subsequent pain NRS questionnaires at home, at approximately the same time each day (recommended between 6pm-10pm). Once lab screening results are available and after completion of at least 7 consecutive days of pain NRS questionnaires, the subject's eligibility to continue to participate in screening (and progress to MRI scan) will be determined.

Eligibility is based on the '24h Average Pain NRS' question (see Appendix 8), taken over 7 consecutive days prior to the assessment. The average of the pain intensity scores over these 7 days is assessed, and an average of '5' or higher (on the 0-10 NRS), is required in order for the subject to be eligible to continue in screening.

If only one hand is affected by HOA and meets the inclusion criteria, the affected hand will be documented at screening and used for all assessments. In cases where both hands are affected by HOA **and both meet the inclusion criteria**, then the dominant hand will be documented at screening and this hand will be used for all MRI assessments throughout the study.

MRI of the affected hand will take place only if the subject has passed all other screening assessments, including all lab assessments and the Pain NRS 7-day assessment. MRI will be the final screening assessment.

All subjects should continue to complete the daily pain NRS questionnaire until all their screening assessments (including MRI) are completed and the final outcome on whether they can participate in the study has been determined. If the subject passes screening and is able to participate in the study, they should continue to complete their daily pain NRS questionnaires until the Week 12 visit has been completed. A final 7 day period of pain NRS questionnaires will then take place in the week prior to the follow-up visit at Week 22.

7.3. Efficacy

Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified at the start of Section 7.

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

Efficacy assessments will include evaluation of hand pain (Pain NRS questionnaire), hand function, pain on use and stiffness (AUSCAN 3.1 NRS), disease activity (patient and physician global assessment of disease activity, PtGA/PhGA), and number of tender, and swollen joints in their hands. For pain efficacy assessments the average pain intensity over 7 days prior to the assessment date will be used. This is calculated from collected daily pain NRS data over the 7 day period prior to the study visit.

7.3.1. Subject's Assessment of Hand Pain, Function, Stiffness, and Subject's / Clinician's Assessment of Global Disease Activity

The patient reported outcome (PRO) questionnaires (Pain NRS, AUSCAN 3.1 NRS, Patient Global Assessment of Disease Activity [PtGA]) will be completed at relevant study visits or at home as described in the Time and Events Table (Section 7.1), and the data entered into the eCRF.

Pain intensity will be assessed by subjects, at home, using a daily Pain NRS (0-10) questionnaire. Subjects will record their 'average hand pain' and 'worst hand pain' intensity over the past 24 hours (see Appendix 8 and Appendix 9), they will also record any use of any rescue paracetamol (acetaminophen) for hand pain over the past 24 hours. This should take place at approximately the same time each day (recommended between 6pm-10pm) for the 12-week treatment period of the study.

Hand function, pain on use and stiffness will be assessed using the AUSCAN Index. Patients will complete the AUSCAN 3.1 NRS at study visits.

A global assessment of disease activity will be completed by subjects and clinicians using a Patient Global / Physician Global Assessment of Disease Activity (PtGA/PhGA) item, which asks subjects / clinicians to rate the level of disease activity today on an 11-point Numeric Rating Scale (NRS, 0-10) with anchors 'Very well' and 'Very Poor' for the PtGA, and anchors 'None' and 'Extremely Active' for the PhGA.

Joint Assessments

To prevent potential bias because of observed efficacy changes, the Joint Assessor must not be the treating physician (PI or sub-investigator) or the unblinded drug administrator.

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

Treating Physician

The Treating Physician (or designee) should be a rheumatologist (or other medically qualified physician) and will have access to both safety and efficacy data. The Treating

Physician will have access to source documents, laboratory results and eCRFs and will be responsible for completing Physician's Global Assessment of Disease Activity, and safety assessments (adverse events, vital signs, concomitant medications, and review of laboratory data).

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

7.4. Safety

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

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

The definitions of an AE or SAE can be found in Appendix 4.

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

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

- 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.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.4.1.2. 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?"

7.4.1.3. 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 7.4.2) 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.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.4.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical dictionary for regulatory activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF 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.

7.4.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. AEs of Special Interest (AESIs)

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

- Serious infections, including serious respiratory infections and tuberculosis.
- Opportunistic infections.
- Neutropenia
- Respiratory events including
    - Pulmonary alveolar proteinosis (PAP).
    - 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
- Hypersensitivity reactions including anaphylaxis.
- Injection site reactions

7.4.3. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until completion of the follow up visit at Week 22.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.4.4. Physical Exams

- A complete physical examination 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 will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.4.5. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.
- Three readings of blood pressure and pulse rate will be taken:
  - First reading should be rejected
  - Second and third readings should be recorded in the eCRF.

7.4.6. Electrocardiogram (ECG)

- Triplicate 12-lead ECGs will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals (based on averaged QTc values of triplicate electrocardiograms obtained over a brief, e.g. 5-10 minute, recording period). Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.4.7. Pulmonary Assessments

Pulmonary assessments are a key aspect of the safety monitoring in this study (refer to Section 5.5.1).

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

- Cough (See Appendix 7).
- Borg CR10 Scale (See SRM for details).
- Lung auscultation.
- Pulse oximetry.
- Pulmonary function tests (PFTs - spirometry, gas transfer [D_{LCO}]).

PFTs will be performed by individual sites. As a general guidance, sites are asked to follow the ATS/ERS recommendations for lung function testing [Miller, 2005a; Miller, 2005b; Macintyre, 2005]. Spirometry should be performed prior to D_{LCO}. Subjects should avoid the following activities prior to undergoing the PFTs:

- Smoking within at least 1 hour of testing
- Consuming alcohol within 4 hours of testing
- Use of bronchodilators within 4 hours of testing
- Performing vigorous exercise within 30 minutes of testing
- Wearing clothing that substantially restricts full chest and abdominal expansion
- Eating a large meal within 2 hours of testing

7.4.8. Immunogenicity

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

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

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

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

7.4.9. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 2, must be conducted in accordance with the Central 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.

All study-required laboratory assessments will be performed by a central laboratory.

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.

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

Table 2 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal) • Urine pregnancy			
Other Screening Tests	• HIV • Hepatitis B surface antigen (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis C (Hep C antibody) • Diagnostic TB test: either QuantiFERON Gold test or T-spot test • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum hCG Pregnancy test (as needed for women of child bearing potential) [2]			

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.1 and Appendix 2.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

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.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

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

Collection, processing, storage and shipping procedures are provided in the Central Laboratory Manual.

7.5.2. Sample Analysis

Serum analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the Central Laboratory Manual. Concentrations of GSK3196165 will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Central Laboratory Manual).

7.6. Biomarkers and Imaging

7.6.1. Magnetic Resonance Imaging

Each subject's affected hand (corresponding to the affected hand which is determined and documented at screening) will be imaged by MRI at screening, week 12 and week 22 (see Section 7.1). If a scanning failure occurs at any visit, if feasible a rescan is allowed within 10 days of the failed scan *after* consultation and agreement with the GSK medical monitor. There will be a minimum of 24 hours between scans where gadolinium contrast is used and any rescan will follow local imaging site regulations for repeat gadolinium administration. The MRI will be used in order to non-invasively quantify the degree of inflammation and structural changes within the target joint.

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

On attendance at the MRI department, subjects will be placed in the scanner and will be prepared for intravenous contrast agent administration. The scanning protocol will

include routine localisers, T1 measurement sequences, dynamic DCE-MRI acquisition, structural scans for bone shape analysis, and acquisitions required for OMERACT HOAMRIS and RAMRIQ scoring. Additional exploratory MRI endpoints, as detailed in the Acquisition Manual, may also be acquired for exploratory purposes.

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

All MRI scans will be reported at the site by a radiologist (non-anonymised) for clinical abnormalities.

7.6.2. Novel Biomarkers

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

Blood samples for novel biomarkers will be collected at the time points indicated in Section 7.1 and processed to plasma (as summarised below). The timing of the collections may be adjusted on the basis of emerging pharmacokinetic or pharmacodynamic (PD) data from this study or other new information in order to ensure optimal evaluation of the PD endpoints.

Collection, processing, storage and shipping procedures are provided in the Central Laboratory Manual.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with osteoarthritis or medically related conditions and/or the action of GSK3196165 may be identified by application of techniques including, but not limited to:

- Biochemical analysis.
- Proteome analysis.
- Metabolomic analysis.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

The results of these biomarker investigations and other exploratory endpoints, may be reported separately from the main study report. This will detailed in the reporting and analysis plan (RAP).

7.7. Genetics

Information regarding genetic research is included in Appendix 3.

7.8. Value Evidence and Outcomes

7.8.1. Post-treatment Interviews

Post-treatment interviews will be conducted as shown in the Time and Events Table (Section 7.1) to explore subjects' experience with study treatment. Post-treatment interviews are qualitative interviews conducted with study subjects to capture subject experiences in drug development on completion of participation in a clinical study. Interview questions designed to fully assess a subject's experience with a study medication are administered in a semi-structured format by a trained interviewer. Subject feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis. The interview technique and questions are described in Appendix 12 and training as well as training material references will be provided to site personnel who will administer the interviews.

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.
- For this study subject data will be collected in electronic GSK defined case report forms (eCRF). For the PRO component, the data will be collected and managed on the modality as determined prior to the start of the study.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary endpoint of the study is to evaluate the change from baseline in 24h average hand pain intensity at Week 6, as measured by daily pain Numerical Rating Scale (NRS) (see Appendix 8) averaged over the 7 days prior to assessment visit with GSK3196165 or placebo in adult subjects with HOA.

The study will test the null hypothesis that there is no difference between GSK3196165 and placebo in the change from baseline in the 24h average Pain NRS at Week 6. The alternative hypothesis is there is a difference between GSK3196165 and placebo in the change from baseline in the 24h average Pain NRS at Week 6 using a two-sided test.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Using a t-test, a sample size of 20 subjects per arm will detect a minimal significant difference over placebo of approximately 2 points in the change from baseline in the 24h average Pain NRS at Week 6 of the 12 week treatment period and has approximately 80% power to detect a difference of 2.7 points assuming an SD = 3 and a 5% significance level. The estimate of variability is based on sample size assumptions from a literature review of two studies in knee OA using a pain NRS [Steigerwald; 2012, Afilalo; 2010].

9.2.2. Sample Size Sensitivity

The power of the study will be affected by changes from the assumed estimate of the SD and Table 3 shows the effect on power and the minimally significant difference under varying estimates of the SD, and the number of subjects needed for 80% power.

Table 3 Power to Detect a Difference -2.7 points for Change from baseline in 24h average Pain NRS at 6 Weeks under Varying Estimates of the SD

SD Estimate	Power with 20 Subjects / arm	Minimal Significant Difference with 20 subjects / arm	N / arm for 80% power
2.5	91%	-1.6	15
3	80%	-2	20
3.5	66%	-2.2	28

9.2.3. Sample Size Re-estimation or Adjustment

No Sample size re-estimation is planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent to Treat (ITT) population: The ITT population is defined as all subjects who were randomised to treatment and who received at least one dose of study treatment. This population will be based on the randomised treatment group.

Safety population: The safety population is defined as all subjects who receive at least one dose of study treatment. This population will be based on the actual treatment received.

Pharmacokinetic (PK) population: The PK population is defined as all subjects who are in the 'Safety' population and who have at least one valid PK assessment.

9.3.2. Interim Analysis

An interim analysis will be performed during the study to review the available PK data and target engagement biomarkers. The timing of this analysis will coincide with other

internal decision making across the GSK3196165 project. Unblinded data will be shared with members of Clinical Pharmacology Modelling and Simulation (CPMS), Clinical Statistics and GSK study team members who have no involvement in the acquisition of the data or direct contact with sites. No other members of the GSK study team will be unblinded to this data.

Another formal interim analysis may be conducted on the key safety, primary efficacy and key secondary endpoints in this study. The purpose of this interim will be to help with decision-making regarding the subsequent clinical development of GSK3196165 for OA. The timing of this analysis will be once a minimum of 30 subjects have completed day 43 (Week 6). Full details will be provided in the RAP which will be available prior to the data being unblinded. Unblinded data will only be shared with selected members of the GSK study team. No members of the GSK study team who have involvement in the acquisition of the data or who have direct contact with the sites will be unblinded to this data.

Recruitment will continue while the interim analyses are being conducted.

For both interim analyses, unblinded summary level data will be available and if required anonymised individual data will be available on request. Only the study pharmacokineticist or study statistician generating the interim analysis results will be unblinded to individual subject treatment allocations.

9.4. Key Elements of Analysis Plan

Full details of all analyses will be provided in the RAP.

9.4.1. Primary Analyses

The primary endpoint will be analysed using a repeated measures model (MMRM) adjusted for baseline pain score, treatment group, visit and the visit by treatment group interaction as fixed effects, patient as a random effect and day within patient as a repeated effect, using an unstructured covariance matrix. The point estimates and corresponding 95% confidence intervals for the treatment differences will be constructed, using the residual error from the repeated measures model. Least squares means and 95% confidence intervals over time for each treatment group will be plotted. Further sensitivity analyses will be conducted to assess the impact of missing data and non-parametric analyses may be conducted if the normality assumption does not hold.

9.4.2. Secondary Analyses

Continuous endpoints will be analysed using the same methods as the primary endpoint.

Binary endpoints, e.g. the proportion of subjects that achieve a 30% reduction in the Pain NRS score from baseline, will be summarised using counts and proportions in remission and analysed using a Generalised Estimating Equation (GEE) model comparing GSK3196165 with placebo at each time point. Subjects with missing Pain NRS scores will be considered as non-responders.

9.4.3. Other Analyses

All safety evaluations will be based on the Safety population. Clinical interpretation will be based upon review and displays of each safety parameter, including adverse events (AE), serious adverse events (SAE) and AEs of special interest. Analyses of AEs by the investigator reported relationship to investigational produce will also be performed.

Full details of all summaries and analyses will be 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 enrolment of subjects begins.

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study (and prior to any wash out time needed to discontinue prohibited medication).
- 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 CRF 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 may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK (or designee) monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. APPENDICES

12.1. Appendix 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
ALT	Alanine transaminase
AMD	Age-related macular degeneration
AST	Aspartate transaminase
ATS	American Thoracic Society
AUC	Area under the curve
AUSCAN	Australian Canadian Hand Osteoarthritis Index
BAL	Bronchoalveolar lavage
βhCG	Beta-subunit human chorionic gonadotropin
BCG	Bacillus Calmette-Guérin
CCP	Cyclic citrullinated peptide
CD4	Cluster of differentiation antigen 4
Cl	Clearance
CL/F	total body clearance from plasma after SC administration
COPD	Chronic obstructive pulmonary disease
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology, Modelling and Simulation
CPPD	Calcium pyrophosphate deposition disease
CRF	Case Report Form
CRP	C-reactive protein
CTC	Common terminology criteria
CV	Cardiovascular
CYP450	Cytochrome P450
DAS28	Disease activity score for 28 different joints
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging
DIP	Distal interphalangeal
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
DMARD	Disease modifying antirheumatic drugs
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European respiratory society
EULAR	European League against Rheumatism
FEV1	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
Gd	Gadolinium
GFR	Glomerular filtration rate
GM-CSF	Granulocyte-macrophage colony stimulating factor
GM-CSFR	Granulocyte-macrophage colony stimulating factor receptor
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B Surface Antigen
HBcAb	Hepatitis B core antibody
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HOA	Hand Osteoarthritis
HOAMRIS	Hand Osteoarthritis Magnetic Resonance Imaging Scoring System
HRCT	High-resolution computed tomography
HRT	Hormone replacement therapy
HV	Healthy volunteer
IB	Investigator's brochure
IC50	The half maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL-6	Interleukin 6
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRE	initial rate of enhancement
IRTS	Interactive response technology system
ITT	Intent to Treat
IV	Intravenous
Ka	absoption rate constant
kg	Kilogram
K^{trans}	exchange rate
L	Litre
LDH	Lactate dehydrogenase
LFT	Lung function test
mAb	Monoclonal antibody
MCV	Mean cell volume
MCH	Mean corpuscular hemoglobin
ME	maximum signal intensity enhancement

MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
MMRM	Mixed model repeated measures
MRI	Magnetic Resonance Imaging
MSDS	Material safety data sheet
NOEL	No observed effect level
NOAEL	No observed adverse effect level
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NSF	Nephrogenic Systemic Fibrosis
NYHA	New York Heart Association
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatology
PAP	Pulmonary alveolar proteinosis
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PFT	Pulmonary function test
PIP	Proximal interphalangeal
PtGA	Patient's Global Assessment
PhGA	Physician's Global Assessment
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PTS-DMPK	Platform Technologies and Science - Drug Metabolism and Pharmacokinetics
QTc	corrected QT interval
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RA	Rheumatoid arthritis
RAMRIQ	Rheumatoid Arthritis Magnetic Resonance Imaging Quantitative Score
RAP	Reporting and analysis plan
RANKL	Receptor Activator of Nuclear factor-κB ligand
RF	Rheumatoid factor
RNA	Ribonucleic acid
SC	Subcutaneous
SAE	Serious adverse event
SRM	Study Reference Manual
t½	Elimination half-life
TB	Mycobacterium tuberculosis
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
v_e	interstitial volume
v_p	plasma volume
Vss/F	total volume of distribution after SC administration

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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12.2. Appendix 2 – Liver Safety Required Actions and 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). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Section 5.4.1.1.) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within a week after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report

treatment and may continue subject in the study for any protocol specified follow up assessments	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

Phase II liver chemistry increased monitoring criteria with continued therapy

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

References

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12.3. Appendix 3 – Genetic Research

Genetics – Background

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

Genetic Research Objectives and Analyses

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

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- HOA susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

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

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

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

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

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

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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:

a. Results in death

b. 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.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

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

12.4.3. 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

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- 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.
- 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.

12.4.5. 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.

12.4.6. 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 GSK Medical Monitor. • 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 or to the GSK Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5 – Contraception eligibility criteria for female and male subjects

12.5.1. Males:

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

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

b. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

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

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

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

12.5.2. Females:

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

a. Non-reproductive potential defined as:

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

- Hysterectomy
- Documented Bilateral Oophorectomy

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

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 12.5.3) 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.

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

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

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

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

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.

12.5.4. Collection of Pregnancy Information (female subjects)

- 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.

12.5.5. Collection of Pregnancy Information (female partners of male subjects)

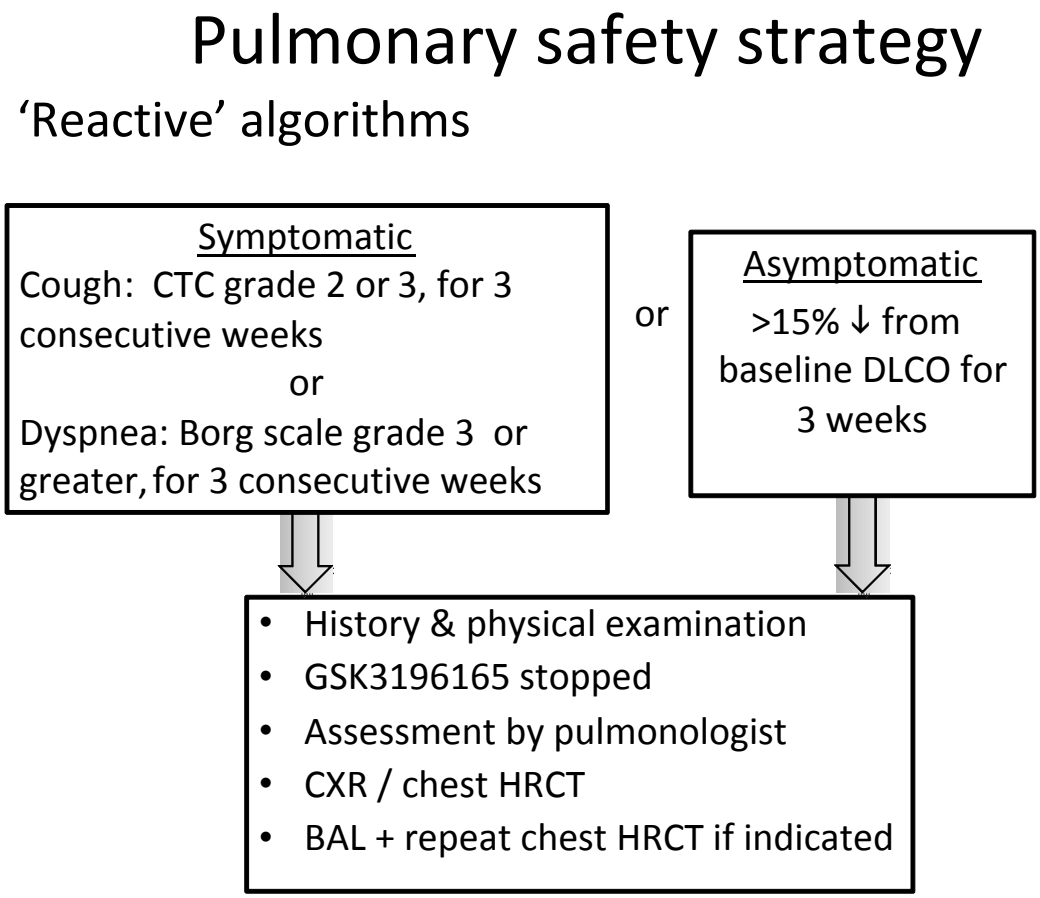
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information 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.

12.6. Appendix 6 – Recommended Pulmonary Assessment Algorithms

12.6.1. Follow-up Algorithms

The following assessment algorithms are recommendations for follow-up triggered by persistent changes in symptoms, spirometry/D_{LCO}, compared with baseline (as detailed in Section 5.5.1). *Note: These procedures are recommendations for the treating pulmonologist, and are not mandatory study procedures.*

	Definition	**Recommended Follow-up**
Symptomatic (Moderate to Severe)	Present for 3 consecutive weeks: • Cough (CTC grade 2 or 3) OR • Dyspnea (Borg CR10 Scale grade 3 or above)	• History, physical examination, and chest X-ray • D_{LCO} measurement If no clear alternative diagnosis can be made, e.g. infection or cardiac failure, then further assessment by a local pulmonologist (including chest HRCT) is recommended: • If HRCT shows ground glass opacity, and no alternative diagnosis, BAL to confirm diagnosis *e.g.* PAP • Repeat chest HRCT 3-6 months later to monitor resolution.
Asymptomatic	Present for 3 consecutive weeks: • Reduction in D_{LCO} >15% relative to baseline value (NB: A subject's baseline D_{LCO} value will be taken as the lowest value obtained from the Screening or Day 1 assessment.)	• Repeat spirometry and two further D_{LCO} (weekly intervals) • If the second or third D_{LCO} returns to a normal range (*i.e.,* change from baseline ≤15%), D_{LCO} should be repeated one week later to ensure stability • If D_{LCO} decrease is persistent: ➢ History & physical examination & chest X-ray ➢ If no alternative diagnosis e.g. infection or cardiac failure, then assessment by a pulmonologist and chest HRCT is recommended • If HRCT shows ground glass opacity, and no alternative diagnosis, BAL to confirm diagnosis *e.g.* PAP • Repeat chest HRCT 3-6 months later to monitor resolution.



12.6.2. Management of Study Medications During Pulmonary Assessment

As described above, study medication should be **withdrawn for the remainder of the study** whilst the subject undergoes these additional pulmonary investigations.

12.6.3. Central Review of Pulmonary Investigations

If a chest HRCT is performed, the HRCT report should be forwarded to GSK and a copy of the images may be requested by GSK and centrally reviewed by a third party.

If the subject undergoes a broncho-alveolar lavage (BAL) assessment, the report should be forwarded to GSK. If biopsies are taken during the BAL procedure, the prepared histologic slides may be requested by GSK for central review by a third party.

On a case-by-case basis, the reports/images/samples from other pulmonary investigations may also be requested by GSK for central review by a third party, and particularly in cases where there is a suspicion of PAP.

12.6.4. Adjudication Process for Suspected Cases of Pulmonary Alveolar Proteinosis

There will be an adjudication process for: 1) all events of PAP, 2) all cases suspicious of PAP, 3) all events that trigger the pulmonary assessment algorithms where an alternative diagnosis cannot be made. GSK may request additional case information (e.g. medical history, imaging data, clinical investigation reports) to assist the adjudication.

The adjudication process will be performed by external experts who are independent of GSK, and will also include independent review of radiological investigations.

12.7. Appendix 7 – Common Terminology Criteria for Adverse Events (CTCAE): Cough

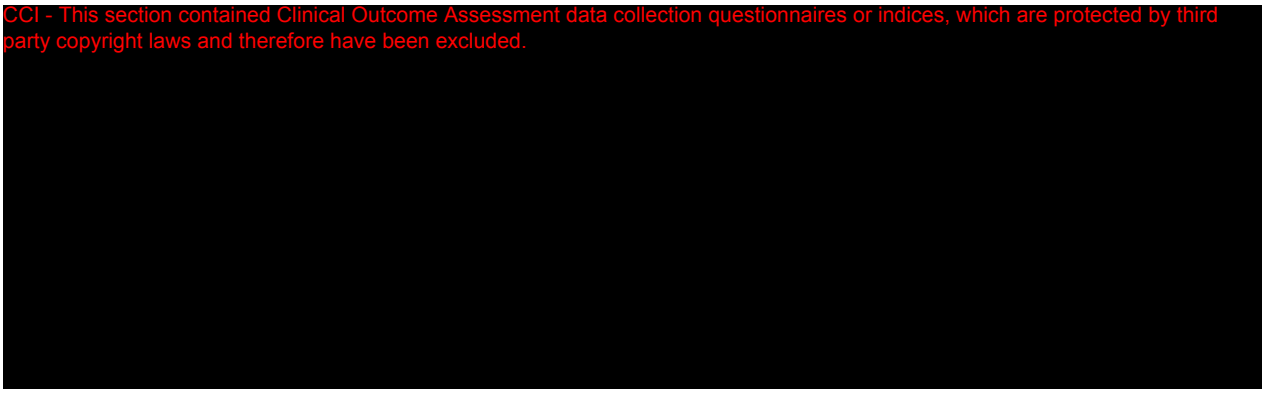
Taken from CTCAE version 4.03 (June 14, 2010): Respiratory, thoracic and mediastinal disorders.

Respiratory, thoracic and mediastinal disorders			
	Grade		
Adverse Event	**1**	**2**	**3**
Cough	**Mild symptoms**; non-prescription intervention indicated	**Moderate symptoms**; medical intervention indicated; limiting instrumental ADL	**Severe symptoms**; limiting self care ADL
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.			

ADL: activities of daily living

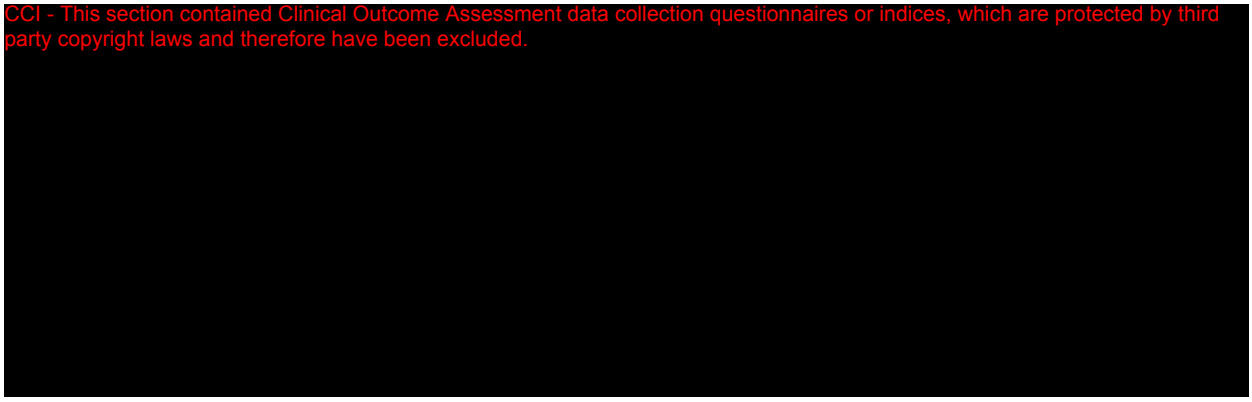
12.8. Appendix 8 – Average Pain NRS

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

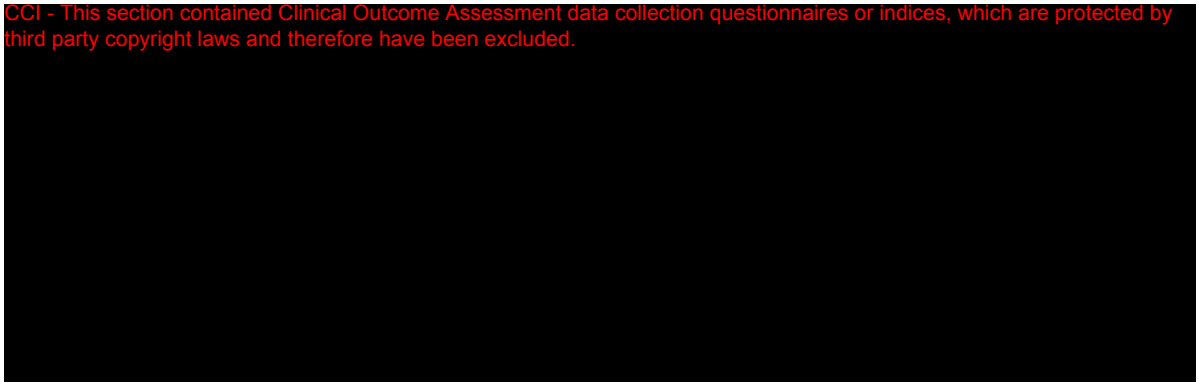


12.9. Appendix 9 – Worst Pain NRS

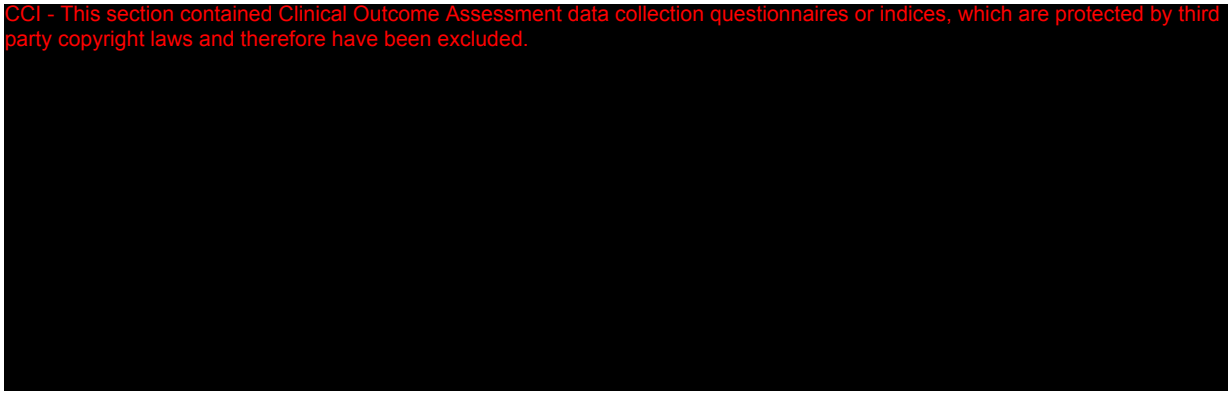
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



12.10. Appendix 10 – Patient Global Assessment of Disease Activity (PtGA)



12.11. Appendix 11 – Physician Global Assessment of Disease Activity (PhGA)



12.12. Appendix 12 – Patient Post-Treatment Interview

Title: A multi-centre Phase IIa double-blind, placebo-controlled study to investigate the efficacy and safety of GSK3196165 in subjects with inflammatory hand osteoarthritis

Patient Post-Treatment Interview

Instructions for Interviewer:

1. At the beginning of the interview, please confirm the patient's study number.
2. Text written in **bold** is to be read verbatim to each subject.
3. Text written in *[italics]* is an instruction to the interviewer.
4. Probes are to be used as needed to encourage the subject to provide full responses to each of the questions. They should be used if the subject gives an incomplete or unclear response or explanation with the initial question.
5. Actively listen during the interview and take notes as necessary.

INTRODUCTION:

Hello, my name is [state first name] and I will be asking you some questions about your experience with medications in this study. The interview will be recorded and a transcript will be developed. In order to protect your confidentiality, only your study number will be included in the transcript. You are free to stop the interview at any time if you decide you no longer wish to participate.

The following questions have been developed to provide information on patient experiences with medications. It is important that you give your best answers, so please listen carefully to each question before you respond.

Are you ready to begin?

[Pause and assess subject readiness to continue]

I will now turn on the recorder. Can you confirm that you agree to have this interview audio-recorded? *[Wait for interviewee to consent; if consent is not provided, end the interview.]*

This is study number 204851, the date is *[state date]***, and I am interviewing participant number** *[state participant number]***.**

1. **Thinking back to when you first entered this study, can you describe the symptoms you were experiencing at that time?**

   [*For each symptom mentioned ask:]*

   1a. [Probe]: **When did you first experience** *[restate symptom]*?
   Was *[restate symptom]* **constant or did it vary/come and go?**
   How long did *[restate symptom]* **last?**
   Please describe the severity of *[restate symptom]*?

2. **Since the beginning of the study, what changes have you experienced?**

   2a. [Probe]: **For example, have you experienced any:**
   Changes in your symptoms?
   New symptoms?
   Changes in how you have been feeling?
   Changes in your ability to do daily activities (wash, dress, eat, household chores)

   [For each symptom/change mentioned:]

   2b. [Probe]: **How did** *[restate symptom]* **change? OR You mentioned a new symptom –can you please describe** *[restate symptom]* **(e.g. onset, frequency, severity, duration), OR You mentioned that the way you were feeling changed. What was this change like? OR You mentioned your ability to do daily activities changed. What was this change like?**

   2c. [Probe]: **On a scale of 0 to 10, where 0 is not at all important and 10 is extremely important, how important was this change to you?What are the reasons you selected X?**

   2d. [Probe]: *[if important]* **What are the reasons this change was important?**

   2e. [Probe]: **Did you experience any other symptoms or changes since starting the study?** *[Ask follow-up probes 2b through 2d above for each symptom / change]*

   2f. [Probe]: **Of the changes you experienced,** *[read back list of changes]***, which was most important to you?**

   2g. [Probe]: **What were the reasons it was most important to you?**

   *2h. [Probe]***: Which change was the next most important?** *[Have participant rank order all remaining symptoms/changes]*

[If patient DOES NOT spontaneously mention each of the following symptoms and changes- pain in their affected hand(s),stiffness in their affected hand(s), swelling in their affected hand(s), ability to do daily activities - ask the relevant questions from questions 3 - 6.]

[If patient DOES spontaneously mention pain in their affected hand(s), stiffness in their affected hand(s), swelling in their affected hand(s), ability to do daily activities move on to question 7.]

3. **Since the beginning of the study, did you have any changes in the pain of your hand(s)?**

   3a. [Probe]: **What were these changes like?**
   3b. [Probe]: **How important were the changes to you?**
   3c. [Probe]: *[If important]* **What were the reasons these changes were important to you?**

4. **Since the beginning of the study, did you have any changes in the stiffness of your hand(s)?**

   4a. [Probe]: **What were these changes like?**
   4b. [Probe]: **How important were the changes to you?**
   4c. [Probe]: *[If important]* **What were the reasons these changes were important to you?**

5. **Since the beginning of the study, did you have any changes in the swelling of your hand(s)?**

   5a. [Probe]: **What were these changes like?**
   5b. [Probe]: **How important were the changes to you?**
   5c. [Probe]: *[If important]* **What were the reasons these changes were important to you?**

6. **Since the beginning of the study, did you have any changes in your ability to perform daily activities (for example: washing, dressing, eating, doing household chores)**

   6a. [Probe]: **What were these changes like?**
   6b. [Probe]: **How important were the changes to you?**
   6c. [Probe]: *[If important]* **What were the reasons these changes were important to you?**

7. **Overall, how satisfied or dissatisfied were you with changes in your symptoms you may have experienced during treatment in this study?**

   [Show the subject the response scale on response scale sheet]

Very dissatisfied	***Dissatisfied***	***Not satisfied or dissatisfied***	***Satisfied***	***Very satisfied***
1	***2***	***3***	***4***	***5***

   7a. [Probe]: **What were the reasons you selected** *[restate response]***?**

8. **How does the medication you received in this study compare to medicines you have taken in the past for your hand arthritis (hand osteoarthritis)?**

   8a. [Probe]: **Do you prefer the study medication or medications you have taken in the past for your hand arthritis (hand osteoarthritis)? What are the reasons you prefer** ***[insert preferred medication]?***

   8b. [Probe]: **What do you like more about the study medication?**

   8c. [Probe]: **What do you like more about your past medications?**

9. **Would you be interested in taking the study medication in the future if it were available?**

[Show the subject the response scale on response scale sheet]

Not at all interested	***A little interested***	***Moderately interested***	***Very interested***	***Extremely interested***
1	***2***	***3***	***4***	***5***

   9a. [Probe]: **What about the study medication makes you interested in continuing to take it?**

   9b. [Probe]: **What about the study medication makes you not interested in continuing to take it?**

   9c. [Probe]: **If there was one thing you could change about the study medication, what would it be? What is the reason you would want to make that change?**

10. **Considering how this study was organized in terms of office visits, lab visits, the patient questionnaires, and in-person and phone conversations with nurses/doctors, what did you like the best about being in the study?**

   *10a. [Probe]:***What is the reason you liked that best?**

   *10b. [Probe]:***What did you like least about being in the study? What is the reason you liked that least?**

   *10c. [Probe]:***Are there any changes you would suggest for future studies to make the experience better for you?**

Thank you for your participation in this interview.

[*Interviewer: Turn off recorder*]

12.13. Appendix 13 – Country Specific Requirements

None

12.14. Appendix 14 – Protocol Amendment Changes

AMENDMENT 01

Where the Amendment Applies

Applicable to all countries and all sites.

Summary of Amendment Changes with Rationale

Correction to contraceptive requirements in Appendix 5, in response to regulatory review comments. Minor correction of question number in post-treatment interview guidance.

List of Specific Changes

Section 12.5.1 Males:

Correction to contraceptive requirements:

ADDED TEXT

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

Section 12.5.3 Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

Correction to contraceptive requirements:

ADDED TEXT

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

Section 12.12 Appendix 12 – Patient Post-Treatment Interview

Minor correction of question number in post-treatment interview guidance Question 2:

PREVIOUS TEXT

[If patient DOES spontaneously mention pain in their affected hand(s), stiffness in their affected hand(s), swelling in their affected hand(s), ability to do daily activities move on to question ~~8~~.]

REVISED TEXT

*[If patient DOES spontaneously mention pain in their affected hand(s), stiffness in their affected hand(s), swelling in their affected hand(s), ability to do daily activities move on to question **7**.]*

AMENDMENT 02

Where the Amendment Applies

Applicable to all countries and all sites.

Summary of Amendment Changes with Rationale

- Amendment of inclusion criteria, #2, #3 and #5, to allow enrolment of subjects who are intolerant to analgesics or NSAIDs, and to remove the requirement that the same joints must be affected at screening and randomization.
- Clarification of exclusion #9 (and Section 7.4.6) to ensure averaged QTc values are used throughout study.
- Amendment of exclusion #19(d) to allow enrolment of subjects with MR-conditional inner ear implants.
- Addition of two planned interim analyses to Section 9.3 and update to planned analysis methods in Section 9.4.
- Update to Time and Events table in Section 7.1.2 and Section 7.1.3, to increase visit Window for Day 3 and to add PK sampling on Day 85 (Week 12 visit) and Day 155 (Week 22 visit).
- Correction to Section 6.10.2 to state that opiate based analgesics must be discontinued at least 22 days prior to Day 1.
- Update to Section 6.4 (Blinding) to allow unblind sponsor staff during interim analyses.
- Correction of Section 4.6, Figure 1, to indicate that follow-up takes place at Week 22.
- Clarification in Section 7, that the requirement to complete PROs before any other assessments applies to assessments at the main study site.
- Update to Section 7.3.1 to clarify which site staff must not be the Joint Assessor.
- Clarification of MRI rescan requirements and increase in the allowed MRI rescan window from 7 to 10 days, in Section 7.6.1.
- Correction of table in Section 12.6.1 to state that the lowest DLCO measurement at screening or baseline is used as the reference for any pulmonary safety monitoring.
- Correction of “Pulmonary Safety Strategy” diagram in Section 12.6.1, removing mention of “MTX”, because this is not used in this study.
- Update of primary and secondary medical monitor details.

List of Specific Changes

Amendment of inclusion criteria, #2, #3 and #5, to allow enrolment of subjects who are intolerant to analgesics or NSAIDs, and to remove

the requirement that the same joints must be affected at screening and randomisation.

PREVIOUS TEXT

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Meets ACR classification of OA and have not responded to analgesics (level 1 and 2) or to NSAIDs for at least 10 days in the past 3 months. 3. Must have active disease at screening and randomization with at least two swollen and tender PIP and/or DIP joints in the affected hand*~~; with the same two joints affected at both screening and randomization.~~ 4. Signs of inflammation such as synovitis in the MRI scan of the affected hand*. 5. Must have a patient's self assessment of 24h average hand pain intensity ~~at baseline~~ of at least '5' on an 11-point NRS (0-10), calculated as an average using data from the 7 days prior to assessment date.

REVISED TEXT

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Meets ACR classification of OA and **is intolerant to, or has** not responded to analgesics (level 1 and 2) or to NSAIDs for at least 10 days in the past 3 months. 3. Must have active disease with at least two swollen and tender PIP and/or DIP joints in the affected hand*. 4. Signs of inflammation such as synovitis in the MRI scan of the affected hand*. 5. Must have a patient's self assessment of 24h average hand pain intensity of at least '5' on an 11-point NRS (0-10), calculated as an average using data from the 7 days prior to assessment date.

Clarification of exclusion #9 (and Section 7.4.6) to ensure averaged QTc values are used throughout study.

PREVIOUS TEXT

9. QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block

REVISED TEXT

9. QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block **based on averaged values of triplicate electrocardiograms obtained over a brief (e.g. 5-10 minute) recording period**

Amendment of exclusion #19(d) to allow enrolment of subjects with MR-conditional inner ear implants.

PREVIOUS TEXT

19. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but not limited to:
    d. Inner ear implants

REVISED TEXT

19. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but not limited to:
    d. Inner ear implants**, except MR-conditional implants scanned within manufacturer guidelines**

Addition of two planned interim analyses to Section 9.3 and update to planned analysis methods in Section 9.4.

PREVIOUS TEXT

9.3 Data Analysis Considerations

9.3.1 Analysis Populations

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

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

9.3.2 Interim Analysis

~~No interim analyses are planned for this study.~~

9.4 Key Elements of Analysis Plan

Full details of all analyses will be provided in the RAP.

9.4.1 Primary Analyses

The primary endpoint will be analysed using a repeated measures model (MMRM) adjusted for baseline pain score, treatment group, visit and the visit by treatment group interaction as fixed effects, patient as a random effect and day within patient as a repeated effect, using an unstructured covariance matrix. The point estimates and corresponding 95% confidence intervals for the treatment differences will be constructed, using the residual error from the repeated measures model. Least squares means and 95% confidence intervals over time for each treatment group will be plotted. Further

sensitivity analyses will be conducted to assess the impact of missing data and non-parametric analyses may be conducted if the normality assumption does not hold.

9.4.2 Secondary Analyses

Continuous endpoints will be analysed using the same methods as the primary endpoint.

Binary endpoints, e.g. the proportion of subjects that achieve a 30% reduction in the Pain NRS score from baseline, will be summarised using counts and proportions in remission and analysed using a ~~logistic regression analysis adjusted for treatment group and baseline Pain NRS score and will be used to test the treatment comparison of GSK3196165 versus placebo. An estimate of the odds ratio, the corresponding p-value and 95% confidence interval will be summarised.~~ Subjects with missing Pain NRS scores will be considered as non-responders.

REVISED TEXT

9.3 Data Analysis Considerations

9.3.1 Analysis Populations

Intent to Treat (ITT) population: The ITT population is defined as all subjects who were randomised to treatment and who received at least one dose of study treatment. **This population will be based on the randomised treatment group.**

Safety population: The safety population is defined as all subjects who receive at least one dose of study treatment. This population will be based on the actual treatment received.

Pharmacokinetic (PK) population: The PK population is defined as all subjects who **are in the 'Safety' population** and who have at least one valid PK assessment.

9.3.2 Interim Analysis

An interim analysis will be performed during the study to review the available PK data and target engagement biomarkers. The timing of this analysis will coincide with other internal decision making across the GSK3196165 project. Unblinded data will be shared with members of Clinical Pharmacology Modelling and Simulation (CPMS), Clinical Statistics and GSK study team members who have no involvement in the acquisition of the data or direct contact with sites. No other members of the GSK study team will be unblinded to this data.

Another formal interim analysis may be conducted on the key safety, primary efficacy and key secondary endpoints in this study. The purpose of this interim will be to help with decision-making regarding the subsequent clinical development of GSK3196165 for OA. The timing of this analysis will be once a minimum of 30 subjects have completed day 43 (Week 6). Full details will be provided in the RAP which will be available prior to the data being unblinded. Unblinded data will only be shared with selected members of the GSK study team. No members of the GSK

study team who have involvement in the acquisition of the data or who have direct contact with the sites will be unblinded to this data.

Recruitment will continue while the interim analyses are being conducted.

For both interim analyses, unblinded summary level data will be available and if required anonymised individual data will be available on request. Only the study pharmacokineticist or study statistician generating the interim analysis results will be unblinded to individual subject treatment allocations.

9.4 Key Elements of Analysis Plan

Full details of all analyses will be provided in the RAP.

9.4.1 Primary Analyses

The primary endpoint will be analysed using a repeated measures model (MMRM) adjusted for baseline pain score, treatment group, visit and the visit by treatment group interaction as fixed effects, patient as a random effect and day within patient as a repeated effect, using an unstructured covariance matrix. The point estimates and corresponding 95% confidence intervals for the treatment differences will be constructed, using the residual error from the repeated measures model. Least squares means and 95% confidence intervals over time for each treatment group will be plotted. Further sensitivity analyses will be conducted to assess the impact of missing data and non-parametric analyses may be conducted if the normality assumption does not hold.

9.4.2 Secondary Analyses

Continuous endpoints will be analysed using the same methods as the primary endpoint.

Binary endpoints, e.g. the proportion of subjects that achieve a 30% reduction in the Pain NRS score from baseline, will be summarised using counts and proportions in remission and analysed using a **Generalised Estimating Equation (GEE) model comparing GSK3196165 with placebo at each time point.** Subjects with missing Pain NRS scores will be considered as non-responders.

Update to Time and Events table in Section 7.1.2 and Section 7.1.3, to increase visit Window for Day 3 and to add PK sampling on Day 85 (Week 12 visit) and Day 155 (Week 22 visit).

ADDED TEXT

Section 7.1.2 Treatment period Time and Events table

Addition of "(± 1d)" window to Day 3 PK biomarker visit.

Addition of a "X" to "PK sampling" row, on Day 85 treatment visit.

Section 7.1.3 Follow-up visit and early withdrawal* procedures list

Addition of "PK sampling" to Subject Follow-up Visit Task List.

Correction to Section 6.10.2. to state that opiate based analgesics must be discontinued at least 22 days prior to Day 1.

PREVIOUS TEXT

6.10.2 Prohibited Medications and Non-Drug Therapies

Use of the medications listed below is prohibited from ~~the start of screening (Screening Day 1, see Time and Events table, Section 7.1)~~ until after completion of the Week 22 follow-up visit.

In addition, these prohibited medications must also be discontinued for the stated time prior to Day 1 as follows:

- Hydroxychloroquine must be discontinued at least 3 weeks prior to Day 1.
- NSAIDs (both systemic and topical) must be discontinued at least 22 days prior to Day 1.
- Opioid based analgesics as well as co-formulated medicines of paracetamol and opioids must be discontinued at least ~~12~~ days prior to Day 1.

REVISED TEXT

6.10.2 Prohibited Medications and Non-Drug Therapies

Use of the medications listed below is prohibited from **Day 1 (randomization)** until after completion of the Week 22 follow-up visit.

In addition, these prohibited medications must also be discontinued for the stated time prior to Day 1 **(randomization)** as follows:

- Hydroxychloroquine must be discontinued at least 3 weeks prior to Day 1.
- NSAIDs (both systemic and topical) must be discontinued at least 22 days prior to Day 1.
- Opioid based analgesics as well as co-formulated medicines of paracetamol and opioids must be discontinued at least **22** days prior to Day 1.

Update to Section 6.4 (Blinding) to allow unblind sponsor staff during interim analyses.

PREVIOUS TEXT

6.4 Blinding

~~The study will be double-blind, which means that the investigator and trial staff at site (apart from the unblinded administrator [study co-ordinator or nurse]), subject, and~~

~~sponsor personnel (apart from unblinded study monitor) will be blinded to the trial treatment allocated to each individual subject.~~

There will be an unblinded administrator (study co-ordinator or nurse) who will prepare and administer the study treatment.

The following will apply.

REVISED TEXT

6.4 Blinding

The study will be double-blind (sponsor unblind), which means that the subject, investigator and trial staff at site (apart from unblinded administrator(s) and pharmacy staff), will be blinded to the trial treatment allocated to each individual subject. In addition, the sponsor central and local study teams will be blinded to treatment allocations, except for roles required to be 'unblind' in order to manage study conduct and oversight (including unblinded monitor(s)) and roles specified in the Reporting and Analysis Plan (RAP) as involved with the preparation and review of the planned interim analyses.

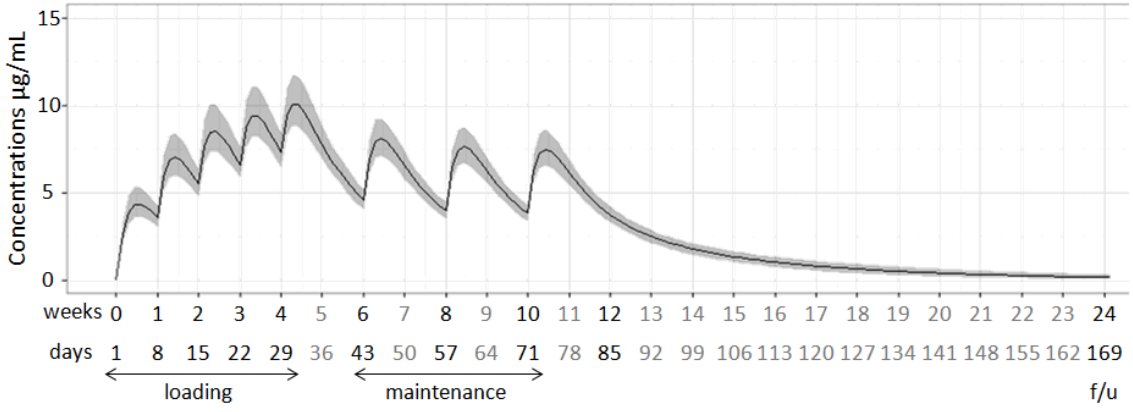
The RAP, which will be approved prior to the first unblinding, will identify the specific GSK individuals involved; outline in detail the activities of the interim analyses, and how the integrity of the study will be maintained.

At sites, there will be at least one unblinded administrator (study co-ordinator or nurse) who will prepare and administer the study treatment.

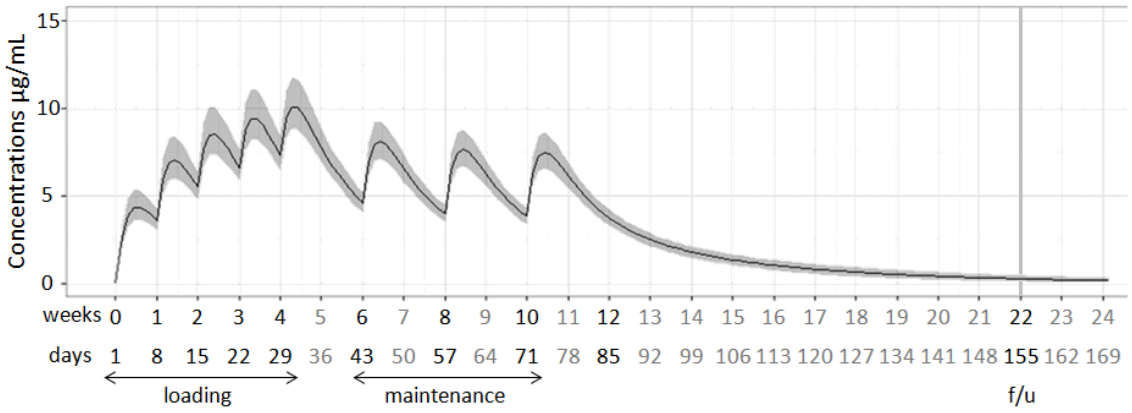
In the case of emergency unblinding (eg. through RAMOS NG or GSK Clinical support help desk), the following will apply:

Correction of Section 4.6, Figure 1, to indicate that follow-up takes place at Week 22.

PREVIOUS FIGURE



REVISED FIGURE



Clarification in Section 7, that the requirement to complete PROs before any other assessments, applies to assessments at the main study site.

PREVIOUS TEXT

- PROs must be administered prior to any other assessments being performed to avoid influencing subjects.

REVISED TEXT

- PROs must be administered prior to any other assessments being performed **(at the main study site)** to avoid influencing subjects.

Update to Section 7.3.1. to clarify which site staff must not be the Joint Assessor.

PREVIOUS TEXT

Joint Assessments

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

REVISED TEXT

Joint Assessments

To prevent potential **bias** because of observed efficacy changes, **the Joint Assessor must not be the treating physician (PI or sub-investigator) or the unblinded drug administrator.**

Clarification of MRI rescan requirements and increase in the allowed MRI rescan window from 7 to 10 days, in Section 7.6.1.

PREVIOUS TEXT

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

REVISED TEXT

Each subject's affected **hand** (corresponding to the affected hand which is determined and documented at screening) will be imaged by MRI at screening, week 12 and week 22 (see Section 7.1). If a scanning failure occurs at any visit, if feasible a rescan is allowed within **10** days of the failed scan after consultation and agreement with the GSK medical monitor. There will be a minimum of 24 hours between scans where gadolinium contrast is used **and any rescan will follow local imaging site regulations for repeat gadolinium administration**. The MRI will be used in order to non-invasively quantify the degree of inflammation and structural changes within the target joint.

Correction of table in Section 12.6.1. to state that the lowest D_{LCO} measurement at screening or baseline is used as the reference for any pulmonary safety monitoring.

PREVIOUS TEXT

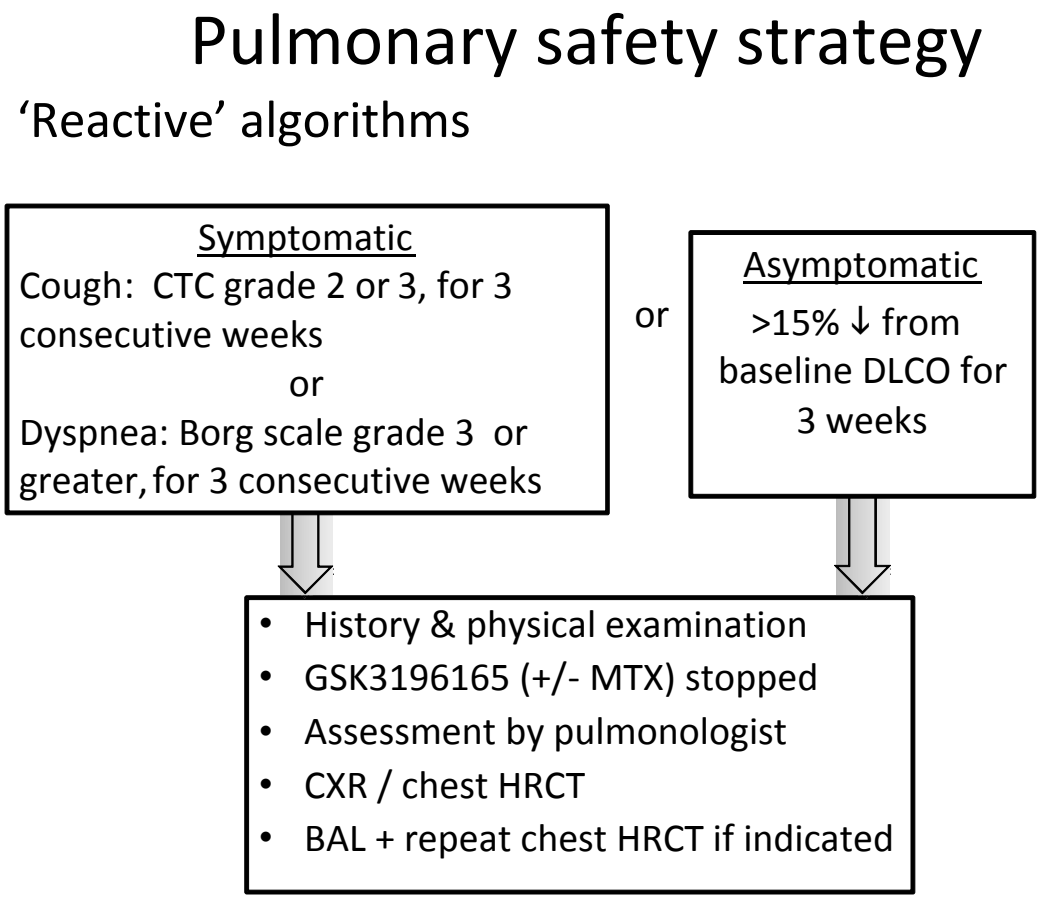
(NB: A subject's baseline D_{LCO} value will be taken as the ~~highest~~ value obtained from the Screening or Day 1 assessment.)

REVISED TEXT

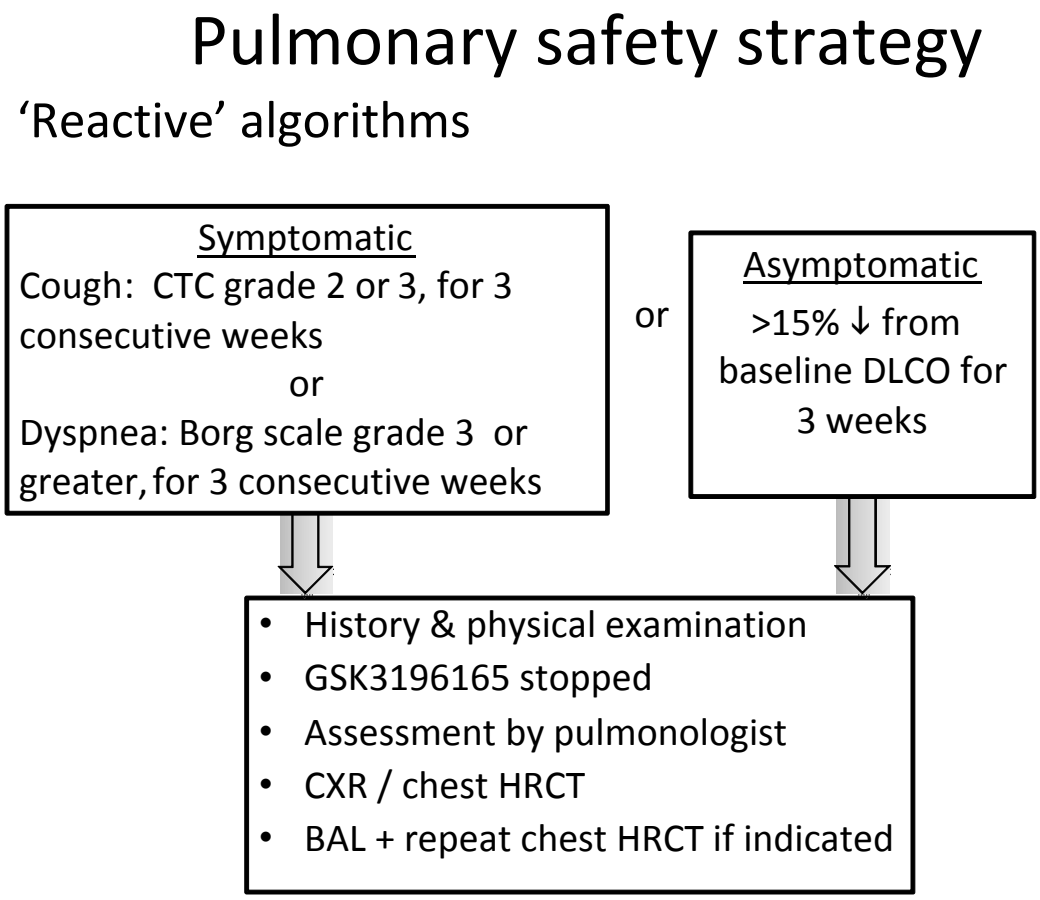
(NB: A subject's baseline DLCO value will be taken as the **lowest** value obtained from the Screening or Day 1 assessment.)

Correction of "Pulmonary Safety Strategy" diagram in Section 12.6.1, removing mention of "MTX", because this is not used in this study.

PREVIOUS FIGURE



REVISED FIGURE



Update of primary and secondary medical monitor details.

PREVIOUS TABLE

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				GSK, Ironbridge Road, Stockley Park West, Uxbridge. UB11 1BT
Secondary Medical Monitor					GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts. SG1 2NY

REVISED TABLE

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts. SG1 2NY
Secondary Medical Monitor					GSK, Ironbridge Road, Stockley Park West, Uxbridge. UB11 1BT