TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised, multi-center, double blind (sponsor open), placebo-controlled study to assess the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of GSK3117391 in subjects with severe, active rheumatoid arthritis

Compound Number: GSK3117391

Development Phase: II

Effective Date: 01-JUN-2017

Protocol Amendment Number: 03

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N270377_00	2016-APR-25	Original
2016N270377_01	2016-JUN-02	Re-Published
Changes made to remove synovial tissue biopsy & correct typographical errors		
2016N270377_02	2016-SEP-15	Amendment No. 1
The changes in this amendment are to address typographical errors and inconsistency between the Time and Events tables (Table 2, Table 3) and the protocol text, particularly with respect to lab parameters (MetHb, coagulation, requirement for clinical chemistry/urinalysis at day 7,14 and 21 and PD biomarkers)		
2016N270377_03	2016-DEC-08	Amendment No. 2
The changes in this amendment are to combine the iSRC and DRC interim review committees, in addition to changes for clarification between the Time and Events table and the text of the protocol.		
2016N270377_04	2017-JUN-01	Amendment No. 3
This amendment has been created to provide clarity regarding extension to the screening window for the washout of background DMARDs, ensuring blinding of the monocyte count during the study conduct, and other study requirements throughout the protocol. In addition, further detail has been added to some of the inclusion/exclusion criteria and assessment requirements for clarification.		

SPONSOR SIGNATORY

PPD

June 1TH 2017

Ramiro Castro-Santamaria, MD, MBA

Date

VP & Head Unit Physician, II TA

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

Regulatory Agency Identifying Number **2015-005800-27**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 204957

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 204957

Rationale

GSK3117391 is a Histone deacetylase (HDAC) inhibitor that uses Esterase Sensitive Motif (ESM) technology to specifically target cells of the mononuclear myeloid lineage. The administered ester is hydrolysed by an intracellular esterase (human carboxy-esterase-1, hCE-1) to its acid GSK3339189 in myeloid cells as a result of the preferential expression of hCE-1 in these lineages. Such targeting of myeloid cells, which play a key role in inflammatory disease, and the consequent reduction in non-myeloid-related side effects should lead to a large therapeutic window. As a result, GSK3117391 has the potential to complement existing therapies in the treatment of chronic inflammatory disorders such as rheumatoid arthritis (RA). This study will evaluate the efficacy, safety and tolerability of 40 mg oral GSK3117391 every other day in subjects with severe RA despite treatment with disease-modifying anti-rheumatic drugs (DMARDs).

Objectives/Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of GSK3117391 in subjects with severe RA following every other day dosing	Change from baseline in Disease Activity Score DAS28-CRP at Day 28
Secondary	
To assess the safety and tolerability of GSK3117391 following every other day dosing	Adverse events Vital signs (HR, BP & Temperature) ECGs Clinical laboratory tests (haematology, biochemistry and urinalysis)
To assess the efficacy of GSK3117391 on other clinical endpoints following every other day dosing	ACR responders (ACR20, ACR50, ACR70) Number of swollen joints assessed using 28-joint counts Number of tender/painful joints assessed using 28-joint counts Change from baseline in DAS28-CRP over time
To assess the pharmacokinetics following every other day dosing of GSK3117391	Plasma concentrations and derived pharmacokinetics (PK) parameters of GSK3117391 and GSK3339189
To investigate the monocyte numbers after every other day dosing with GSK3117391	Changes in monocyte numbers over time
To assess the effects of GSK3117391 on biomarkers of inflammation in the blood	Changes from baseline in blood biomarkers, including but not limited to: C-reactive protein (CRP), Soluble cytokine and inflammatory mediators Myeloid-related protein 8/14 (MRP8/14)

Overall Design

This is a randomised, double-blind (sponsor open), multicentre, placebo-controlled, parallel group study to evaluate the efficacy, safety and tolerability, PK and PD of GSK3117391 in subjects with RA resistant to DMARD therapy.

Treatment Arms and Duration

The total maximum study duration is approximately 10 weeks (not including any rescreen). Following a screening period of up to 28 days, or up to 56 days, if required only for the washout of background DMARD therapy, subjects will be randomised (1:1) to placebo or 40 mg GSK3117391 orally-administered every other day for a period of 28 days. Subjects will be followed up for 7-14 days post final dose.

Type and Number of Subjects

Approximately 40 subjects with severe RA despite treatment with DMARDs will be randomised into the study.

Analysis

Hypotheses and Treatment Comparisons: The study will evaluate the effect of GSK3117391 relative to placebo on the change from baseline in DAS28-CRP after 4 weeks of treatment. The primary analysis will test the null hypothesis of no treatment effect against the alternative hypothesis that that there is a difference in DAS28-CRP change from baseline between the active and placebo groups using a Mixed effect Model for Repeated Measures (MMRM), adjusting for baseline DAS28-CRP score. A secondary analysis of the primary endpoint will use the Bayesian framework to determine posterior probabilities of the difference in DAS28-CRP change from baseline between the treatment groups.

Sample Size Calculations: The properties of DAS28-CRP based on historical variability data and the 20 subjects randomised to each study arm are outlined in Section 9.2.

Interim analysis: An interim analysis of difference in change in DAS28-CRP may lead to a decision to stop the study for futility.

2. INTRODUCTION

2.1. Study Rationale

This study will evaluate the efficacy, safety and tolerability of 40 mg oral GSK3117391 every other day in subjects with severe RA. In addition, the effects on monocytes seen in the first time in human study (201302) will be evaluated further. Furthermore, this study will enable the exploration of pharmacokinetics (PK) and pharmacodynamics (PD) using every other day dosing, as results from study 201302 have shown that once daily dosing appears to result in higher levels of the acid form of GSK3117391 (defined as GSK3339189) being retained in monocytes than may be necessary for maximal pharmacological engagement.

2.2. Brief Background

Histone deacetylase (HDAC) inhibitors have been shown to be active in various models of inflammation (Lin, 2007; Nishida, 2004; Joosten, 2011; Glauben, 2008) and to have anti-inflammatory activity in clinical studies (Vojinovic, 2011; Furlan, 2011). However there is a concern that, because of their pleiotropic activity, it may be challenging to obtain a therapeutic window wide enough to allow their extensive use in the treatment of inflammatory disorders such as RA.

GSK3117391 is an HDAC inhibitor that uses Esterase Sensitive Motif (ESM) technology, whereby an ester is hydrolysed by an intracellular esterase to a more polar acid which accumulates in cells that express carboxy-esterase-1 (hCE-1). GSK3117391 is selectively hydrolysed to the active acid, GSK3339189 by hCE-1, which is predominantly expressed in myeloid cells, leading to selective accumulation of GSK3339189 in cells of that lineage (such as monocytes, macrophages and dendritic cells). Using ESM technology to target myeloid cells, which play a key role in inflammatory disease, should lead to consequent reduction in non-myeloid-related side effects allowing a greater therapeutic window. As a result, GSK3117391 has the potential to become an extremely important agent in the treatment of chronic inflammatory disorders such as RA.

RA is an inflammatory joint disease where macrophages and monocytes become activated and infiltrate the synovial membranes, secreting inflammatory cytokines such as tumour necrosis factor (TNF) α and interleukins (IL) -1, -6 and -8 (Li, 2013). These cytokines activate fibroblast-like synoviocytes which produce enzymes that damage the bones and cartilage. DMARDs are the fundamental treatment for patients with RA. Methotrexate (MTX) is the gold standard treatment and it effectively reduces clinical disease measures in a large proportion of patients. However, only 30% of RA patients will have low disease activity with MTX alone and in the population failing to respond, combination treatment with biological DMARDs targeted to cytokines, B-cells or T-cells, is the preferred option (O'Dell, 2013). A subset of these patients will still fail to achieve meaningful responses to treatment, or experience adverse events (AEs), and will continue to experience severely debilitating symptoms (Rubbert-Roth, 2009). Therefore, there continues to be a current unmet need for more effective treatments for RA with novel mechanisms of action in patients refractory to conventional and biological DMARDs. As

an orally active, myeloid-targeted small molecule, GSK3117391 represents an attractive alternative to the currently approved anti-cytokine antibodies and non-selective, oral anti-inflammatory agents, such as Janus Kinase (JAK) inhibitors.

In the first clinical study with GSK3117391 (201302; GlaxoSmithKline Document Number 2014N193968_00 26-MAY-2015 A Phase I Double-Blind, Randomised, Placebo-controlled, Dose Escalating Study to Assess the Safety and Tolerability of Single and Multiple Oral Doses of CHR-5154 and the Effect of the Fasted and Fed State on Pharmacokinetics of CHR-5154 and CHR-5426 in Healthy Male Volunteers), cohorts of healthy volunteers received oral doses of GSK3117391 either as single ascending doses up to 60 mg or as multiple ascending doses of up to 40 mg once daily for 7 days. This study characterised the PK of GSK3117391 and its acid GSK3339189. No clinically significant adverse events were observed and GSK3117391 was well tolerated. A decision was made to stop the study prior to proceeding to the final repeat dose cohort following the emergence of an unexpected PD effect, namely a depletion of circulating monocytes that was observed following both single and multiple doses. Importantly, this effect was transient and reversible with no observed clinical effects and was not associated with any adverse events or Dose Limiting Toxicities (DLTs).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the efficacy of GSK3117391 in subjects with severe RA following every other day dosing	Change from baseline in DAS28-CRP at Day 28
Secondary	
To assess the safety and tolerability of GSK3117391 following every other day dosing	Adverse events Vital signs (HR, BP & Temperature) ECGs Clinical laboratory tests (haematology, biochemistry and urinalysis)
To assess the efficacy of GSK3117391 on other clinical endpoints following every other day dosing	ACR responders (ACR20, ACR50, ACR70) Number of swollen joints assessed using 28-joint counts Number of tender/painful joints assessed using 28-joint counts Change from baseline in DAS28-CRP over time Note that components of composite endpoints (ACR response, DAS28-CRP) at all assessment timepoints will also be reported separately.
To assess the pharmacokinetics following every other day dosing of GSK3117391	Plasma concentrations and derived pharmacokinetics (PK) parameters of GSK3117391 and GSK3339189
To investigate the monocyte numbers after every other day dosing with GSK3117391	Changes in monocyte numbers over time

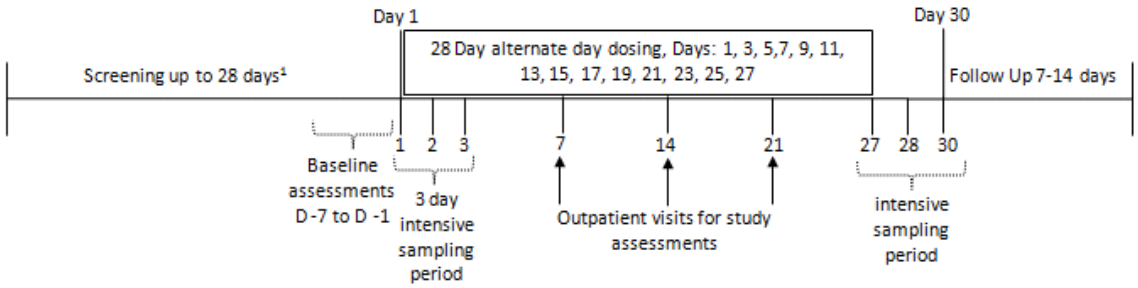
Objectives	Endpoints
To assess the effects of GSK3117391 on biomarkers of inflammation in the blood	Changes from baseline in blood biomarkers, including but not limited to: C-reactive protein (CRP), Soluble cytokine and inflammatory mediators Myeloid-related protein 8/14 (MRP8/14)
Exploratory	
To assess the intracellular pharmacokinetics following every other day dosing of GSK3117391	Where possible, intracellular concentrations and derived PK parameters of GSK3339189 following every other day repeat doses
To evaluate the PD of GSK3117391 following every other day dosing	Acetylation levels in monocytes, lymphocytes and granulocytes in peripheral blood
To explore the effects of GSK3117391 on the leukocyte population	Cell marker quantification using flow cytometry
To investigate the effect of GSK3117391 on inflammatory gene expression in blood	Change from baseline in inflammatory gene expression in blood

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind (sponsor open), multicentre, placebo-controlled, parallel group study to evaluate the efficacy, safety and tolerability, PK and PD of GSK3117391 in subjects with severe RA resistant to DMARD therapy. Approximately 40 subjects will be randomised to either GSK3117391 or placebo to be taken every other day for 28 days of treatment. In addition to weekly visits for safety and efficacy assessments, subjects will be intensively sampled after the first and final doses to allow for thorough investigation of the PK and PD effects of GSK3117391. The maximum total duration of the study is approximately 10 weeks from screening to the last study visit. See Figure 1 for a study schematic.

Figure 1 Study schematic



[1] The screening window can be extended for up to 56 days to allow only for the washout of background DMARD therapy if necessary

4.2. Treatment Arms and Duration

4.2.1. Screening

All subjects must provide written informed consent for the study prior to the start of screening period. Subjects will be screened up to 28 days prior to the Day 1 visit (randomisation and start of the treatment period). The screening window can be extended for up to 56 days to allow only for the washout of background DMARD therapy if necessary (see Section 6.11.2 for washout periods for DMARD therapies and other medications). Subjects on medications requiring longer washout than 56 days prior to Day 1 must have discontinued medication for the stated washout time in Section 6.11.2 before being considered for eligibility in this study.

All other screening assessments must be performed within 28 days prior to Day 1(dosing Day 1).

4.2.2. Treatment Period

Subjects will be randomised to either GSK3117391 or placebo in a 1:1 ratio, i.e. 20 subjects per arm. Treatment will be taken once every other day for a period of 28 days (14 doses), in accordance with the randomisation schedule generated prior to the start of the study using validated internal software.

During the treatment period, subjects will return to the clinical site for visits on Days 1-3, 7, 14, 21, 27, 28 and 30. On these visit days, subjects should not take study treatment prior to the visit. Subjects will be given a diary card and instructed to take study medication every other day, recording this and any adverse event in the diary card.

4.2.3. Follow up period

After the treatment period, the subject enters the follow up period for 7 to 14 days.

4.3. Type and Number of Subjects

Approximately 40 subjects will be randomised. This assumes a dropout rate of approximately 15%.

4.4. Design Justification

This study is designed to assess the efficacy, safety and tolerability of alternate day dosing of GSK3117391 in RA subjects. This is the first study of GSK3117391 in patients. An additional objective of this study will be to characterise the pharmacokinetic profile of GSK3117391 and its acid, GSK3339189, and to determine pharmacodynamic effects in this population.

Subjects in this study are not currently benefiting from DMARD therapy therefore such DMARD therapies will be excluded for the duration of the study. Any subject currently deriving benefit from DMARD therapy will not be included in this study.

Inclusion of a placebo group is to provide a control for comparison of subjects treated with GSK3117391 and to allow robust exploration of the safety profile of GSK3117391. Inclusion of placebo will also allow measurement of the comparable effect of GSK3117391 and determination of DAS28 reduction and the ACR20 response rates. The treatment duration of 28 days will minimise the exposure to placebo in the study. If a subject experiences an unacceptable level of disease activity during the study, the investigator may withdraw the subject from further study treatment at any point. The subject is then to enter the follow up period, where subject will be able to receive standard of care treatment at the discretion of the investigator as early as 7 days after the last dose of study medication.

The study is sponsor open to enable members of the Data Review Committee (DRC) to be unblinded for the planned interim analyses of safety data (including clinical laboratory parameters and AEs), monocyte counts and efficacy (see Section 9.3.2 and Section 10.8.2). The interim analysis of efficacy will be conducted once an appropriate number of subjects complete day 30 assessments. As a consequence of this efficacy analysis the study may be stopped for futility, according to the futility criteria outlined in the DRC charter. However it is not planned to stop the study as a result of the interim analysis of monocyte counts.

4.5. Dose Justification

Subjects in this study will be treated with 40 mg of GSK3117391 every other day for a 28 day period. This dose is justified by the safety, PK and PD profile of the molecule:

In Study 201302, the PK of GSK3117391 was well characterised. The plasma half-life where could be estimated, was consistent across doses (i.e. 20, 40, 50 and 60 mg), with the geometric mean in single administration ranging between 0.343h and 0.500h, while the geometric mean of the half-life of its acid, GSK3339189, in plasma ranged between 0.604h and 0.767h. Small to minimal accumulation ratios were observed in repeat administration regimens. The plasma half-life of both GSK3117391 and GSK3339189 were found to be shorter than their sustained intracellular effect (manifested as prolonged increases in both cellular acetylation and inhibition of cytokine production after *ex vivo* LPS stimulation of sampled blood).

After single dose administration, sustained average intracellular concentrations of acid GSK3339189 within monocytes were observed above its IC_{50} (18.0 ng/mL or 53.83nM) at 12h post-dose with doses of 10 mg or higher (minimum average concentration 134.6 ng/mL for the10mg dose). In addition, the intracellular acid levels were also above the IC_{90} (308.35 ng/mL or 920.45nM) for at least 4h following doses of 40 mg and above (average concentrations of 429.7ng/mL of monocytes at 4h post-dose for the 40mg dose). Consistent with this intracellular target engagement, selective acetylation of monocytes was maintained for at least 12 hours in this study.

In Study 201302, a decrease in the monocyte count was observed 4 hours post-dose and was enhanced by repeat administration, but the count had returned to baseline in all but one subject by the post-study follow up visit which was performed between 4 and 7 days after the last study drug administration. Monocytopaenia was not accompanied by any

clinical signs or symptoms and was not associated with any AEs or DLTs. There were no other clinically significant myeloid or non-myeloid adverse events observed in subjects after repeat doses up to 40 mg.

Therefore, a dose of 40 mg administered with a less frequent regimen than the one investigated in the previous clinical study has the potential to maintain efficacy while also allowing a higher extent of monocyte recovery during each dosing interval**.** An every other day dosing strategy for a 28 day period has been proposed, which limits the number of doses to 14. An appropriate sampling scheme will be utilised to fully characterise the monocyte profile as well as levels of acetylation and other mechanistic biomarkers.

4.6. Benefit: Risk Assessment

4.6.1. Risk Assessment

Potential Risk of clinical significance	Mitigation Strategy
Potential haematologic toxicity (Including monocytopaenia)	
Following single doses of up to 60 mg GSK3117391 and repeat doses up to 40 mg GSK3117391 in healthy volunteers there was a trend for a decrease in the absolute monocyte counts. Levels generally returned to baseline values by 4-7 days post-dose. There was no evidence from the FTIH study 201392 in healthy volunteers of an increased incidence of infection. In a study in healthy volunteers, one subject had minor changes in haemoglobin. No changes in monocyte numbers were observed in definitive 4 week studies in rat and cynomolgus monkey. In contrast, *increased* monocyte numbers were observed in cynomologus monkeys at higher dose levels in the dose range finding studies. Monocytopaenia was observed in hCE1/Es1e-BP8 transgenic mice which express a complementary copy of the human carboxyesterase-1 gene under the control of the CD68 promoter. Minor haematological changes were observed in rats and cynomolgus monkeys. Where assessed, effects were not observed after an off-dose period. Effects on the thymus were observed in the rat dose range finding study (decreased cellularity) and 28 day monkey study (decreased thymic weight and thymic atrophy).	**Subject selection** – Subjects with abnormal haematological parameters will be excluded from the study. In addition, subjects with active infections, or a history of recurrent infections, or with previous exposure or past infection with Mycobacterium tuberculosis, HIV or Hepatitis B or C will also be excluded. **Subject Monitoring** – Monocyte and other white blood cell numbers will be monitored during the study. There will also be close monitoring of the subjects for infections.. **Withdrawal Criteria** -Haematological stopping criteria have been added to the protocol. Subjects who develop a serious infection will also be withdrawn from study treatment.

Potential Risk of clinical significance	Mitigation Strategy
Reproductive and development	
In preliminary embryofoetal development studies, dose-related reproductive and developmental toxicity (up to complete pre- and post-implantation loss, and decreased foetal body weight) was seen in the rat and rabbit. At all doses, there were skeletal abnormalities/variations and delayed ossification (both species), with foetal malformations (predominantly cardiovascular) being observed in the rabbit. Systemic exposure at the lowest effect levels are below/approximately at parity to the anticipated exposure for a 40 mg dose of GSK3117391. Evaluation in a number of studies concluded that GSK3117391 is an aneugen with a NOEL at 60 mg/kg (sc) in the rat bone marrow micronucleus study. The rat NOEL for aneugenicity provides 35-fold and 10.6 fold cover for the anticipated AUC and Cmax, respectively, for a 40 mg dose in human. Syncytia in the seminiferous tubules was observed in one male at 10 mg/kg/day. Although this could be a background finding, the severity suggests it is treatment related.	**Subject Selection** – In this study, subjects must agree to specific contraceptive guidelines and precautions for males and females which are provided in the protocol. In addition, the informed consent will include potential reproductive risks and precautions in addition to recommendations for the maintenance of the fertility potential. Male subjects will be required to avoid donating sperm or conceiving a child for the duration of the study until 91 days after the last dose. **Subject Monitoring** – Female subjects will be tested for pregnancy before during and after the study. In additon, pregnancies of female partners of male subjects in the study will be followed if consent is given. **Withdrawal Criteria** – Any female subject who becomes pregnant will be withdrawn from the study.
Clotting disorders	
Minor changes relating to coagulation (increase in activated partial thromboplastin time and prothrombin time) were evident in rats. Not seen to date with GSK3117391 clinically.	**Subject Selection** – Subjects with a history of clotting, or on current anti-coagulant treatment e.g.warfarin, will be excluded from the study. **Subject Monitoring** – The protocol includes monitoring of clotting parameters e.g. INR/APTT & platelet count will occur throughout the study. Supportive therapy will be provided according to standard medical practice. **Withdrawal Criteria** – Platelet number stopping criteria have been added to this protocol.
Gastrointestinal events	
Rats and monkeys exhibited reduced food consumption and body weight loss. In the rats non-adverse histological effects (minimal to mild in severity) were observed in the duodenum (inflammation, mucosal atrophy, degeneration of villous epithelium and increase in mitotic figures). Marked ulcerative inflammation was found in the oesophagus of two monkeys given 10 mg/kg/day in the 4 week study. Both had loss of condition (dehydration, body	**Subject Selection** – A body weight of $\geq$ 45 kg is required for subjects to be included in this study. Appropriate exclusion criterion regarding a history of pre-existing gastrooesophageal ulcers is included in this study protocol. **Subject Monitoring** – During clinical studies clinical history, physical examination (including weight) and clinical laboratory assessments will be used to identify and assess toxicity in the gastrointestinal tract. Gastrointestinal AE/SAEs will be monitored. **Withdrawal Criteria** – In the event of clinically significant GI toxicity, study treatment will be

Potential Risk of clinical significance	Mitigation Strategy
weight loss, subdued) and one of these animals was terminated on Day 9 as a result. The oesophageal ulceration was likely a contributing factor in the demise of this animal. These effects may be due to dosing trauma and/or irritation from formulation, although were not seen in the vehicle control group.	discontinued and supportive therapy provided according to standard medical practice.
Potential drug-drug interactions	
GSK3117391 has been shown to be an inhibitor of CYP2C8 and CYP3A4 *in vitro*. A risk assessment using physiological based pharmacokinetic modeling suggests the clinical risk of DDI with CYP2C8 substrates is negligible. A similar assessment with for CYP3A4 suggests risk of DDI is weak. *In vitro*, GSK3117391 is cleared predominately *via* CYP3A4 and esterases with the latter playing the predominate role *in vivo*. The clinical risk of CYP mediated DDIs is low.	Use of concomitant medications, herbal medicines and fruit juices that are strong CYP3A4 inhibitors or inducers will be prohibited.
Exacerbations of RA	
Common risk for this patient population is the recurrent exacerbations of RA (these may vary in severity).	Subjects will be monitored & treated by qualified investigators for any AEs/SAEs/exacerbations using permitted medications as per protocol. If appropriate, subjects will be withdrawn from the study in consultation with the Medical Monitor and referred to their respective GP/specialist consultant and/or Rheumatology clinics at the discretion of the Investigator or Designee.

4.6.2. Benefit Assessment

Histone deacetylase (HDAC) inhibitors have been shown to be active in various models of inflammation (Lin, 2007; Nishida, 2004; Joosten, 2011; Glauben, 2008) and to have anti-inflammatory activity in clinical studies (Vojinovic, 2011; Furlan, 2011); therefore it is anticipated that GSK3117391 may show some benefit in subjects with RA. In addition, the FTIH study demonstrated that the drug engaged with the target and produced *ex vivo* PD effects in inflammatory cytokines as detailed in the Investigator Brochure (GSK Document Number 2014N201956_00 GSK3117391 Investigator's Brochure. 22-APR-2016) . There is an unmet need for therapies in the RA population. Subjects will benefit from thorough medical assessments as part of the study procedures and will have regular access to medical care for the duration of the study.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential risks identified in association with GSK3117391 are justified by the anticipated benefits that may be afforded to subjects with RA.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability and/or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. The subject must have a diagnosis of RA as an adult (≥18 years) according to the 2010 ACR/EULAR classification criteria for RA.
3. Functional class I, II or III defined by the 1992 ACR Classification of Functional Status in RA
4. The subject must have a EULAR DAS28-CRP of greater than 5.1 at screening.
5. Disease duration of >6 months (time from onset of patient-reported symptoms of either pain or stiffness or swelling in hands, feet or wrists).

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
6. Swollen joint count of ≥6 (66-joint count) and tender joint count of ≥8 (68-joint count) at screening and at day 1 7. The subject must have a CRP serum level of ≥ 5 mg/L at screening 8. The subject has had an inadequate response or intolerance of DMARDs (due to lack of efficacy or toxicity, after at least 8 weeks treatment).

WEIGHT
9. Body weight ≥ 45 kg and body mass index (BMI) within the 18.5 - 35 kg/m^2 inclusive.

SEX
10. Male or female requirements. **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 91 days after the last dose of study medication. Male condom plus recommendation for partner to use of one of the contraceptive options as detailed in Appendix 2. This is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on that provided by the ICH [ICH M3 (R2), 2009]." In addition male subjects must not donate sperm for 91 days after the last dose of study medication. The investigator is responsible for ensuring that subjects understand how to use these methods of contraception properly. **Females**: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative human chorionic gonadotrophin (hCG) 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.

SEX
• 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]). NB - 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. Females of reproductive potential must have proper and established use of a Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 2) from 28 days prior to the first dose of study medication and until 15 weeks after the last dose of study medication and completion of the follow-up visit. In addition subjects will be required to utilise a barrier method of contraception. A negative serum hCG pregnancy test at the first screening visit and urine hCG pregnancy test (with a sensitivity of at least 25 IU/L) at the following visits: between Day-7 to -4, on Day 1 prior to first study medication dose administration, at the weekly study visits, and the follow up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception and receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures.

INFORMED CONSENT
11. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Pregnant or lactating women.
2. Subjects who meet diagnostic criteria for any other rheumatic disease (e.g., lupus erythematosus, gout, psoriatic arthritis).
3. Subjects who have previously been treated with more than 1 biologic agent (such as TNF inhibitors and their biosimilars eg. adalimumab, etanercept, infliximab, certolizumab, golimumab or non-TNF inhibitors and their biosimilars eg.abatacept, rituximab, tociluzimab) or any investigational biologic.
4. Subjects with past history of granulomatous disease eg leprosy, sarcoidosis.
5. Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, haematological (including clotting disorders), gastrointestinal (including gastrooesophageal ulcers), pulmonary, cardiac (including ischemic heart disease), neurological, or cerebral disease, or other medical conditions that, in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study.
6. Subjects with any values for monocytes are below the lower limit of normal (LLN) at screening.
7. Haemoglobin <11 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm^3 (≤3.0 x 10^9/L) or ≥14,000/mm^3 (≥14 x 109/L); platelet count ≤ 100,000/μL (≤100 x 109/L); absolute neutrophil count ≤2 x 10^9/L; lymphocyte count <1 x 10^9/L at screening.
8. ALT and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
9. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
10. QTcF or QTcB > 450 msec (based on the average of triplicate ECGs) at screening.
11. Abnormal findings on ECG considered clinically significant by the investigator.
12. A history of carcinoma in situ and malignant disease, except for adequately treated non-invasive cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
13. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
14. Abnormal chest X-ray within 12 weeks of Day 1 (locally read and reported by a radiologist) judged by the investigator as clinically-significant.
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:

- Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
- Hospitalisation for treatment of infection within 12 weeks of Day 1.
- Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 12 weeks of Day 1 or oral antimicrobials within 14 days of Day 1.

17. 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.

18. 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.

CONCOMITANT MEDICATIONS

19. The subject has received treatment with the therapies listed in Section 6.11.2 or changes to those treatments in the prescribed timeframe. Subjects who have previously taken >1 biologic therapy for RA are excluded from this study. Note: Subjects who have taken one biologic therapy only with a documented lack of response are eligible.

20. Other medications (including vitamins, herbal and dietary supplements) will be considered on a case-by-case basis, and will be allowed if in the opinion of the investigator the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS

21. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

22. Smokers who would not be able to refrain from smoking whilst in the clinic.

23. Subjects who cannot refrain from consuming any of the following fruits or juices (alone or in combination): seville oranges, grapefruit, pummelos, or any citrus fruits from 7 days prior to the first dose of study medication until their discharge from the unit after their last dose of study medication.

CONTRAINDICATIONS
24. History of sensitivity to any components of the study medication, or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
25. Serologic evidence of current/previous Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg) and anti-Hepatitis B core (anti-HBc) antibody as follows within 6 weeks of Day 1: Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded
26. Hepatitis C: Positive test for Hepatitis C virus (HCV) antibody confirmed on a subsequent blood sample by RNA-polymerase chain reaction (PCR) assay within 6 weeks of Day 1. Subjects who are positive for Hepatitis C antibody and negative for Hepatitis C RNA-PCR assay performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for Hepatitis C RNA-PCR assay performed on the subsequent sample,will not be eligible to participate.
27. A positive test for HIV 1 or 2 at screening.
28. Evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following: a. No history of active or latent TB infection irrespective of treatment status b. A negative diagnostic TB test within 28 days of baseline (Day 1) defined as: i. A negative QuantiFERON Gold test or T-spot test (two successive indeterminate QuantiFERON tests will be considered as a positive result). OR ii. If QuantiFERON gold or T-spot test not approved or registered in country of participation, then a negative tuberculin skin test (TST) reaction as per local guidelines is required (it is strongly recommended that subjects with a history of Bacillus Calmette-Guérin (BCG) vaccination be tested with QuantiFERON gold test). c. Chest X-ray within 12 weeks of Day 1 with no evidence of current or previous pulmonary tuberculosis, locally read by a radiologist.
29. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
30. Participation in a trial with any investigational drug within 3 months or 5 half-lives (whichever is longer) before the start of the study and within 4 months if the study drug was new chemical entity. Exposure to more than 3 new chemical entities in a clinical study setting within 12 months prior to the first dosing day.
31. Donation of blood in excess of 500 mL within a 56 day period prior to dosing.

5.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to 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 (SAE's) (see Section 7.5.1.5).

5.3.1. Re-Screening

Re-screening is permitted with the approval of the medical monitor if a subject has not met the Eligibility Criteria within the screening period with the following exception:

- If a subject fails screening due to Exclusion Criteria 6 and/or 7 in Section 5.2, rescreening is not permitted.

Subjects are only allowed to be re-screened once; the entire screening process must be repeated.

Chest X-ray does not need to be repeated during re-screening, if one was conducted within 12 weeks of re-screening Day 1 and showed no evidence of current or previous pulmonary tuberculosis, locally read by a radiologist.

Repeat testing of glucose-6-phosphate dehydrogenase (G6PD) deficiency during rescreening is not needed, if test result during original screening was negative.

If a blood sample has to be redrawn due to sample handling problems, breakage or sample integrity, this is not considered a re-screening. Further details regarding the procedure for re-screening may be found in the Study Reference Manual (SRM).

5.3.2. Re-Testing

5.3.2.1. Laboratory Tests

If the investigator is not able to assess subject's eligibility for any of the laboratory exclusion criteria in cases of (a) technical malfunction (e.g. loss of laboratory specimen); (b) an indeterminate result or (c) if there is reason to believe the result may be false (i.e. contradicts recent result for the same parameter) the test may be repeated once within the screening period after consultation with the medical monitor. If the original result was exclusionary and is confirmed by repeat testing then the subject is to be considered a screen failure; these subjects may be re-screened as described in Section 5.3.1.

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

5.3.2.2. Electrocardiogram (ECG) Test

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

The triplicate electrocardiogram (ECG) may be repeated once within the screening period if the recorded QTc value was slightly out of range, and the Investigator does not consider that there are any other clinically-significant findings

5.4. Withdrawal/Stopping Criteria

Subjects may be withdrawn from the study for any of the following reasons:

- 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. 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. The reason for withdrawal should be documented in the eCRF.
- The Sponsor's request, for reasons such as significant protocol deviations (and after discussion with the investigator).
- Study is terminated by the Sponsor.

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

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

Any subject who does not complete the study will have a follow up visit, to occur 7-14 days post withdrawal.

5.4.1. Individual Safety Stopping Criteria

Study medication will be discontinued in the event of any of the following:

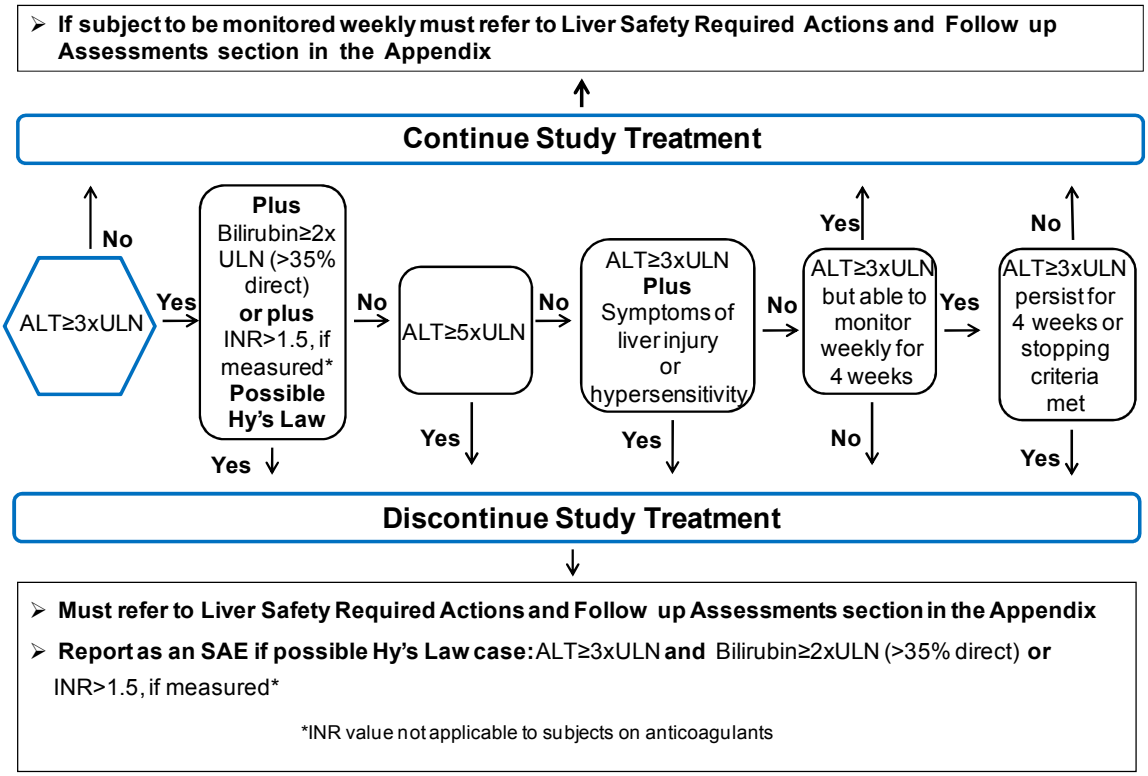
- If a subject experiences a serious or severe clinically significant AE that in the clinical judgement of the investigator, after consultation with the Medical Monitor, is possibly, probably or definitely related to investigational product.
- The subject becomes pregnant.
- The subject initiates treatment with any prohibited medication for the treatment of RA as listed in Section 6.11.2.
- The subject develops a serious infection.
- If the liver chemistry stopping criteria (Section 5.4.2), QTc stopping criteria (Section 5.4.3), or Haematologic stopping criteria (Section 5.4.4) are met Group Safety Stopping Criteria

In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subjects will be regularly reviewed by the Sponsor Safety Review Team (SRT) and/or the DRC in order to ensure appropriate subject safety. Any changes to the study due to safety reasons will be promptly communicated to the appropriate Regulatory Authorities.

5.4.2. 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 3

5.4.2.1. 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.

5.4.3. 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 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

5.4.3.1. Study Treatment Restart or Rechallenge

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

5.4.4. Haematologic Stopping Criteria

Study treatment will be stopped for a subject if any of the following haematological stopping criteria is met:

- Haemoglobin < 9 g/dL (5.58 mmol/L) or an absolute decrease of ≥3 g/dL from baseline (pre-dose Day 1)
- Neutrophils < 1 x 10^9/L
- Lymphocytes < 0.5 × 10^9/L
- Platelets < 50 × 10^9/L

5.4.4.1. Study Treatment Restart or Rechallenge

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

5.5. 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 trial is defined as the last clinic visit (follow up visit) of the last subject in the trial. Completion of the trial globally is required in order to provide sufficient subjects as defined in Section 9.2, Sample Size Determination.

A subject who withdraws from treatment will be withdrawn from the study, and will attend a follow up clinic visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment	
Product name:	GSK3117391	Placebo
Dosage form:	Capsule	Capsule
Unit dose strength(s)/Dosage level(s):	20mg	N/A
Storage requirements	Store refrigerated (2 – 8°C)	Store refrigerated (2 – 8°C)
Route of Administration	Oral	Oral
Dosing instructions:	2 capsules in the morning every other day	2 capsules in the morning every other day
Physical description:	White opaque, gelatin capsule	White opaque, gelatin capsule
Method for individualising dosage:	Capsule packed in separate HDPE bottles	Capsule packed in separate HDPE bottles

6.2. Treatment Assignment

At Screening a unique CRF number (subject number) will be assigned to any subject who has at least one Screening procedure performed, other than informed consent. The unique subject number will be used to identify individual subjects during the course of the study.

Subjects who meet screening eligibility criteria and complete the pre-treatment assessments will be randomised to a treatment group through an Interactive Response Technology (IRT). The IRT will confirm the subject's CRF number (subject number) and provide the randomisation number using the randomisation schedule.

The study will use central randomisation and the randomisation schedule will assign subjects to GSK3117391 or placebo in a ratio of 1:1. The randomisation schedule will be generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Once a randomisation 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.

6.3. Planned Dose Adjustments

There will be no dose adjustments in this study.

6.4. Blinding

The study will be double-blind (sponsor open), where the investigator and trial staff at site, subject and most sponsor personnel will be blinded to the trial treatment allocated to each individual subject and interim results. Sponsor open refers only to the DRC (a limited set of central GSK study team members who will be involved in the review of data as defined in Section 10.8.2) and senior GSK stakeholders. A limited number of project team members may be informed of the results of interim analyses where relevant to their activities. The DRC charter will identify the specific GSK individuals involved and will outline in detail the activities of these reviews, and how the integrity of the study will be maintained. The rest of the central GSK study and project team members will remain blinded.

The trial will be blinded by means of allocation via IxRS, and using a placebo to match which will be kept in cold chain conditions as per active IP.

The anticipated effect of GSK3117391 on monocyte count and CRP may unblind a subject's treatment allocation to any reviewer. As a consequence, monocyte count data and CRP (both of which will be analysed in a central laboratory) will not be available to the site during the study after screening. Investigators will, therefore, be blinded to the monoctye count but will be able to view other WBC counts. Summary monocyte counts for all subjects will be reviewed by the SRT once sufficient subjects have been recruited to avoid unblinding. Individual level monocyte count and CRP data will only be reviewed by the DRC.

PK, PD, biomarker and exploratory leukocyte data will also not be available to the central study team until the end of study apart from for the DRC specified in Section 10.8.2.

To prevent potential unblinding because of observed efficacy changes, a "dual assessor" approach will be used with different assessors evaluating efficacy and safety (as specified in Section 7.3.2.2.

Although a subject may be withdrawn from the study if that subject's treatment assignment is unblinded, data collected prior to the unblinding event may be used in analysis.

Unblinding of individual subjects may occur to ensure appropriate management of subject, eg if an SAE is considered by the PI as being causally related to study drug, taking account of the points below.

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

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required. The study treatment must be stored refrigerated (2-8^{o}C) at site, and at subject's home.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorised 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 authorised 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 Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions will be provided to the investigator, where required by local laws, or is otherwise available upon request from GSK.

6.7. Compliance with Study Treatment Administration

When subjects self-administer study treatment(s) at home, compliance with every other day administration of the assigned GSK3117391 or placebo capsules will be assessed through querying the subject during the site visits and documented in the source documents and CRF. Sites will call subjects on non clinic visit dosing days to remind them to take their study treatment. A record of the number of GSK3117391 /placebo capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates and times, including dates for treatment delays and/or dose reductions will also be recorded in the patient diary. If a subject misses a dose, they will be instructed to take it as soon as possible within 24 hours of the scheduled dose. If they have not taken it within 24 hours of the scheduled dosing time then they should continue with future doses as scheduled (i.e. they should not alter their planned dosing time).

Only subjects with appropriate compliance will be included in the per-protocol population for the primary analysis. To be compliant the subject must not miss more than one dose per interval between site visits. If a subject misses a dose in more than two between-visit intervals then they will be considered non-compliant. Subjects who take one additional dose on more than one occasion will also be considered non-compliant with the protocol.

6.8. Treatment of Study Treatment Overdose

For this study, more than 4 capsules of the study medication within a 26 hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator or treating physician should:

- Contact the Medical Monitor immediately to determine whether the subject may continue in the trial and what (if any) additional assessments need to be made.

- Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until the end of the study.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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 other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

Subjects must refrain from consuming any of the following fruits or juices (alone or in combination): seville oranges, grapefruit, pummelos, or any citrus fruits from 7 days prior to the first dose of study medication until their discharge from the unit after their last dose of study medication.

6.10.2. Caffeine, Alcohol, and Tobacco

Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) may not be permitted while they are in the clinic.

6.11. Concomitant Medications and Non-Drug Therapies

All medications and non-drug therapies will be recorded as concomitant medication. Rescue with conventional DMARDs or biologics is not allowed in this study. Every effort should be made to keep the subject on study treatment with no change in background medication unless the subject experiences an excessive disease flare that, in the investigator's opinion, warrants a change in therapy.

6.11.1. Permitted Medications and Non-Drug Therapies

The following medications are permitted for the treatment of RA.

6.11.1.1. Oral Corticosteroids

Continued use of oral corticosteroids ≤10 mg/day prednisone or equivalent is allowed if the dosage was stable for at least 4 weeks prior to screening.

6.11.1.2. NSAIDs

Continued use of NSAIDs is permitted (i.e. diclofenac, ibuprofen, ketoprofen, naproxen, celecoxib and etoricoxib etc) in daily doses up to the maximum recommended according to locally accepted clinical practices if the dosage was stable for at least 2 weeks before screening. The concomitant use of proton pump inhibitors, e.g. omeprazole or pantoprazole, is strongly recommended in order to lower the risk of complications affecting the gastrointestinal tract caused by NSAIDs.

If the patient is not regularly using NSAIDs, he/she may take the NSAIDs mentioned above as breakthrough pain management. However, subjects should be advised not to take any NSAIDs within 12 hours prior to attending a trial visit.

6.11.1.3. Analgesics

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

6.11.1.4. Other

Medications used to treat conditions other than RA (and not listed in Table 1 below, or in the eligibility criteria) may be used at the discretion of the investigator, in consultation with the Medical Monitor if needed.

6.11.2. Prohibited Medications and Non-Drug Therapies

Table 1 Prohibited throughout the study, from the time periods stated until after 7 days from the last dose of the study medication:

Drug class	Examples	Washout time prior to dosing
Any conventional DMARDs (if not listed here please contact medical monitor)	Hydroxychloroquine, sulphasalazine, minocycline, cyclosporin	At least 2 weeks prior to Day 1
	Methotrexate, azathioprine	Discontinue ≥28 days prior to Day 1
	Leflunomide	Leflunomide must be discontinued ≥8 weeks prior to Day1 if no elimination procedure is followed. Or discontinued with the following elimination procedure ≥4 weeks prior to Day 1: Cholestyramine at a dosage of 8 g three times daily for at least 24 hours, or activated charcoal at a dosage of 50 g 4 times a day for at least 24 hours.
	Gold salts	26 weeks prior to Day 1
Targeted biological DMARDs	Anakinra	1 week prior to Day 1

Drug class	Examples	Washout time prior to dosing
	Etanercept	Discontinue for at least 2 weeks prior to Day 1
	Adalimumab, infliximab	Discontinue for at least 8 weeks prior to Day 1
	Certolizumab pegol, golimumab	Discontinue for at least 10 weeks prior to Day 1
	Abatacept, tocilizumab	12 weeks prior to day 1
	Rituximab, belimumab and other B cell depleting agents	1 year and a normal CD19/20 cell count as measured by flow cytometry.
Targeted synthetic DMARDs	Tofacitinib Baricitinib	At least 2 weeks prior to Day 1
NSAIDS	Diclofenac, ibuprofen, ketoprofen, naproxen	New or change of dose within 14 days of Day 1
Corticosteroids	Prednisolone, dexamethasone IM, IV, IA PO	 Within 8 weeks of Day 1 Any treatment with >10 mg/day dose oral prednisolone (or equivalent) within 28 days of Day 1. New oral corticosteroid or changes in corticosteroid dose within the 28 days prior to Day 1.
	Plasmapheresis or intravenous immunoglobulin (IVIg) or use of Staph protein A column (Prosorba)	26 weeks prior to Day 1
Any investigational treatment		Must be discontinued for at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1
Strong inhibitors and inducers of CYP3A4 (unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.)	Rifampicin, phenytoin, carbamazepine, St Johns Wort, amprenavir, atazanavir, clarithomycin, conivaptan, itraconazole, ketoconazole, ritonavir, nelfinavir, fosamprenavir, grapefruit juice, indinavir, voriconazole, telithromycin, saquinavir.	Within 7 days prior to the first dose; or 14 days if the drug is a potential enzyme inducer prior to first dose
Alkylating agents	Cyclophosphamide or chlorambucil	Discontinue >=8 weeks prior to Day 1
Agents which may cause haemolytic anaemia	Methyldopa	Subjects taking methyldopa are not eligible for this study
	Cephalosporin	From 7 days prior to Day 1 and throughout the study until follow up
Anticoagulant therapy	Warfarin	Subjects taking Warfarin will not be eligible for this study

6.11.2.1. Complementary Therapies

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

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables, is 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 Tables Section 7.1

The following points must be noted:

- If assessments are scheduled for the same nominal time, then the assessments should, where possible, 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, 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/Independent Ethics Committee (IRB/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 600 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

Table 2 Screening and Follow-up Assessments

Procedure	**Screening** (up to 28 days prior to Day 1[1])	**Follow-up Visit** (7-14 days post last dose or EW[2])	***Notes***
			1. Screening period can be extended to 56 days to allow ONLY the washout of background DMARD therapy where necessary. All other assessments must be completed within 28 days prior to Day 1. Some assessment can occur on separate visit 2. For EW (Early Withdrawal) visit, assessments are to be conducted as deemed necessary based on PI's judgment and to be recorded as a unscheduled visit in the subject's CRF
Outpatient Visit	X	X	Additional screening visit needed for FRP pregnancy test 4 to 7 days before day 1
Informed Consent	X		Informed consent must be obtained prior to any study procedures being conducted including DMARD therapy washout period.
Medical/medication/drug/alcohol history	X		
Demographics	X		
Height and weight	X		
Full Physical Examination	X		Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).
Brief Physical Examination		X	
Eligibility criteria	X		
12-lead ECG and vital signs	X	X	Vital signs include HR, BP and temp.
Pregnancy test	X	X	First test in screening is serum pregnancy test, all subsequent testing urine. An additional pregnancy test during screening visit (urine) is required 4-7 days prior to Day 1. FRP only.
Contraception use compliance	X	X	
HIV, Hep B and Hep C screen, TB, G6PD	X		
RF, ACPA (i.e. aCCP)	X		
Haem/Chem/Urinalysis tests	X	X	Including INR/APTT (coagulation) and MetHb (MetHb, performed locally)
PK blood sample and MetID		X	Sample to be collected only if the 24h-post last dose sample (at D28) has not been collected
PD biomarker sample		X	This includes biomarkers for RA disease and exploratory PD, acetylation
HAQ-DI, PtGA, PtAAP	X	X	Complete before any other assessment at a clinic visit

Procedure	**Screening** (up to 28 days prior to Day 1[1])	**Follow-up Visit** (7-14 days post last dose or EW[2])	***Notes***
			1. Screening period can be extended to 56 days to allow ONLY the washout of background DMARD therapy where necessary. All other assessments must be completed within 28 days prior to Day 1. Some assessment can occur on separate visit 2. For EW (Early Withdrawal) visit, assessments are to be conducted as deemed necessary based on PI's judgment and to be recorded as a unscheduled visit in the subject's CRF
Joint counts: TJC(68), SJC(66)	X	X	Independent joint assessor
Physician Global Assessment of Arthritis (PhGA)	X	X	Where possible, the same physician should perform all disease assessments for an individual subject.
hs-CRP	X	X	
Chest x-ray	X		Only required at screening if no CXR performed within 12 weeks of Day 1 visit
Adverse Event Review		X	
Concomitant Medication Review		X	
Gene expression blood		X	

Table 3 Day 1 to Day 30 On-Study Assessments

	D1								D2	D3						D7[2]	D14[3]	D21[2]	D27							D28	D30
Study treatment every other day including clinic visit days as shown	X									X						X		X	X								
Time in relation to dose[1]	pre	0.25h	0.5h	1h	2h	4h	6h	10h	24h[4]	pre	0.25h	0.5h	1h	4h	8h	pre		pre	pre	0.25h	0.5h	1h	2h	4h	6h	10h	24h[4]	72h[4]
12 lead ECG and vital signs	X					X		X	X					X		X	X	X	X								
Brief physical examination	X														X	X	X	X	X							X	X
Pregnancy test (FRP)	X															X	X	X	X								
Contraception use compliance	X								X	X						X	X	X	X							X	X
Haematology test	X			X		X	X	X	X	X			X	X	X	X	X	X	X			X		X	X	X	X	X
Chem/Urinalysis test	X							X	X	X						X	X	X	X								
Coagulation (INR/IPTT)	X							X	X	X						X	X	X	X							X	X
Joint counts: TJC(68), SJC(66)	X															X	X	X								X	
Patient reported outcomes[5] PtGA, PtAAP, HAQ-DI	X															X	X	X								X	
PhGA	X															X	X	X								X	
hs-CRP	X															X	X	X								X	
RF, ACPA	X																										
MetHb																	X									X	
RA disease biomarker blood	X			X[6]		X[6]		X[6]	X[6]	X[6]					X[6]	X	X	X	X[6]							X	
Exploratory PD and acetylation blood	X			X		X		X	X	X			X	X	X	X	X	X	X			X		X		X	X	X

	D1								**D2**	**D3**						**D7[2]**	**D14[3]**	**D21[2]**	**D27**								**D28**	**D30**
Study treatment every other day including clinic visit days as shown	X									X						X		X	X								
Time in relation to dose[1]	pre	0.25h	0.5h	1h	2h	4h	6h	10h	24h[4]	pre	0.25h	0.5h	1h	4h	8h	pre		pre	pre	0.25h	0.5h	1h	2h	4h	6h	10h	24h[4]	72h[4]
PK blood	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MET ID blood	X	X	X	X	X	X	X	X	X										X	X	X	X	X	X	X	X	X	
Isolated monocyte PK[7]	X			X		X		X	X	X			X	X	X				X			X		X		X	X	X
Gene expression blood	X																											
PK urine sample	X	Collect urine for 24h after dose																										
PGx	X																											
Drug compliance assessment[8]																X	X	X	X									
AE and concurrent med review	Collect AE's from D1 to end of follow up visit																											

FRP, Females of reproductive potential; HAQ-DI, Health Assessment Questionnaire Disability Index; hs-CRP, high sensitivity C-reactive protein; INR/IPTT, International normalised ratio/partial thromboplastin time; PhGA, Physician Global Assessment of Arthritis; PtGA, Patient Global Assessment of Arthritis; TJC, Tender Joint Count; SJC, Swollen Joint Count; PtAAP, Patient Assessment of Arthritis Pain; ACPA, Anti-citrullinated protein antibodies; RF, rheumatoid factor; PK, pharmacokinetics ; PGx, pharmacogenomics.

1. Sample collection and assessments to be conducted in accordance with the time and events table.
2. Visits may be conducted on previous or next DOSING day.
3. The D14 visit has a ± 2 day window and may be on a DOSING or NON DOSING day. If on a dosing day, assessments should be per formed pre-dose.
4. Blood samples to be collected within a ±1h window of the scheduled time.
5. Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit.
6. Sample will be collected and stored for future analysis.
7. Applicable to selected sites only.
8. Record number of capsules in bottle and check patient diary. On non-visit days, phone subject to remind them to take dose .

7.2. Screening and Critical Baseline Assessments

Screening and eligibility criteria are as listed in T&E Tables and Section 5, respectively.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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

Critical baseline measures include: DAS28-CRP score, ACR criteria, HAQ-DI, and exploratory biomarkers.

Disease activity assessments (screening and baseline):

- Patient reported outcomes
    - HAQ-DI which includes an item on pain severity during the past week
    - Patient's Assessment of Arthritis Pain.
    - Patient's Global Assessment of Arthritis.
- Tender/Painful Joint Count (68 joints).
- Swollen Joint Count (66 joints).
- Physician's Global Assessment of Arthritis.

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

Procedures conducted as part of the subject's routine clinical management, e.g. blood count or chest X-ray and obtained prior to signing of informed consent may be utilised for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

The investigator is responsible for ensuring that subjects understand how to properly use contraception methods detailed in Appendix 2 and receive continued guidance during screening and study conduct with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the followings:

- Contraceptive requirements of the study
- Assessment of subject compliance through questions such as
    - Have you forgotten to use contraception since the last visit?
    - Is there a chance you could be pregnant?

7.3. Efficacy

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

Efficacy assessments will include Health Assessment Questionnaire – Disability Index (HAQ-DI – physical function,), Patient's assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, evaluation of all 68 joints for tenderness and 66 joints for swelling (to be performed by an independent joint evaluator), Physician's Global Assessment of Arthritis and laboratory assessments (including CRP). Based on these assessments ACR (20, 50 and 70), DAS28-CRP and the EULAR response will be calculated by the central GSK team.

7.3.1. Patient Reported Outcomes

Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit.

7.3.1.1. Disability Index of the Health Assessment Questionnaire (HAQ-DI)

The functional status of the subject will be assessed by means of the Disability Index of the Stanford Health Assessment Questionnaire (HAQ-DI). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas [Fries, 1980]: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities.

The HAQ-DI will be utilised to assess the subject's physical function or disability according to the subject. The study staff should not clarify any of the questions for the subject.

The HAQ-DI will be used to calculate ACR responders.

7.3.1.2. Patient's Assessment of Arthritis Pain (PtAAP)

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

Further details of this assessment are provided in the SRM.

7.3.1.3. Patient's Global Assessment of Arthritis (PtGA)

Subjects will complete a global assessment of disease activity using the patient global assessment (PtGA) item, a VAS with anchors "0" (very well) to "100" (very poor). This forms part of the ACR response and DAS28 assessments. This assessment will be used to calculate ACR responders.

Further details of this assessment are provided in the SRM.

7.3.2. Joint assessments

The procedure for joint assessments can be found in the SRM. Tender Joint Counts (TJC) and Swollen Joint Counts (SJC) form part of the ACR and DAS28 measurements.

7.3.2.1. Replaced or Fused Joints

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

7.3.2.2. Independent Joint Evaluator

To prevent potential unblinding because of observed efficacy changes, a "dual assessor" approach will be used with different assessors evaluating joints.

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

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

It is essential that assessments completed by the subject and joint assessor are made before those by the treating physician.

7.3.3. Physician's Global Assessment of Arthritis (PhGA)

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

Further details of this assessment are provided in the SRM.

7.3.4. Measurement of Serum CRP

Blood samples will be collected in order to measure serum CRP concentrations. This forms part of the ACR response and DAS28-CRP assessments.

7.4. Derived measurements

7.4.1. DAS28 measurements

The DAS28 is a derived measurement with differential weighting given to each component. The DAS28-CRP will be calculated at each assessment timepoint.

The components of the DAS28 arthritis assessment include:

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

Sites/investigators will not have access to ongoing DAS28 scores, apart from the screening visit results (needed to confirm eligibility).

7.4.2. ACR measurements

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

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

- Health Assessment Questionnaire – Disability Index (HAQ-DI) which includes an item on pain severity during the past week.
- Patient's Assessment of Arthritis Pain.
- Patient's Global Assessment of Arthritis.
- Tender/Painful Joint count (assessment of 68 joints).
- Swollen Joint Count (assessment of 66 joints).
- Physician's Global Assessment of Arthritis.
- CRP

7.5. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables (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.

All subjects will return for a follow-up visit 7 to 14 days after last dose of study medication

7.5.1. 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.

7.5.1.1. 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 Day 1 until the follow-up contact (see Section 7.5.1.3), at the timepoints specified in the Time and Events Tables (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 CRF.
- 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.

7.5.1.2. 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 enquire 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.

7.5.1.3. 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 4.6.1) will be followed until resolution, until the condition stabilises, 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.

7.5.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 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.

7.5.1.5. 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, IRB/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.

7.5.2. Pregnancy

- Details of all pregnancies in female subjects, and female partners of male subjects if available, will be collected after the start of dosing and until 91 days post study.

- 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 4.

7.5.3. 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, skin and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.5.4. 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. The first reading should be rejected, while the second and third readings should be averaged to give the measurement to be recorded in the CRF

7.5.5. Electrocardiogram (ECG)

12-lead ECGs will be obtained in triplicate at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Additional repeat ECG measurements may be taken if required. Refer to Section 5.4.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.5.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. 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 laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments that are performed at the institution's local laboratory result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) their results must be recorded in the CRF. Investigators should note that due to the anticipated effect of GSK3117391 on monocyte count, any local WBC panel assessments may unblind a subject's treatment allocation to any reviewer. Therefore, every effort should be made to ensure that local monocyte count data is not available to the site during the study. Investigators will however be able to view total WBC counts and differential WBC counts that do not include monocyte counts.

Refer to the SRM 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 4.

Table 4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	Reticulocytes			
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit	MCHC	Monocytes	
	INR/APTT		Eosinophils	
	MetHb		Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
	CRP			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• G6PD • HIV • Hepatitis B (HBsAg) • HBcAb • Hepatitis C (Hep C antibody) • QuantiFERON-TB • Rheumatoid Factor (RF), ACPA • FSH and estradiol (as needed in females of non-child bearing potential only) • 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 5.4.2 and Appendix 3.
2. Central laboratory serum pregnancy test for the first visit during screening. Local urine testing for all other subsequent visits will be standard for the protocol unless serum testing is required by local regulation or ethics committee.
3. The following parameters will only be performed at selected time points as per Time and Events Table: INR, MetHb, CRP.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study 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.

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK3117391 and its acid metabolite GSK3339189 will be collected at the time points indicated in Section 7.1,

Time and Events Tables. Additional samples will be collected for investigation of other compound-related metabolites (MET ID) as indicated in Section 7.1, Time and Events Tables.

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.

Processing, storage and shipping procedures are provided in the investigators manual. 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.

Processing, storage and shipping procedures are provided in the laboratory investigators manual.

7.6.2. Urine Sample Collection

Urine samples (pre-dose and 0-24h) will be collected for investigation of GSK3117391, GSK3339189 and other compound-related metabolites.

Details of urine collection, sample processing, storage and shipping procedures are provided in the laboratory investigators manual.

7.6.3. Monocyte isolation

Where possible, monocytes will be isolated from blood samples for pharmacokinetic (PK) analysis of GSK3339189 at the time points indicated in Section 7.1, Time and Events Tables. 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. Processing, storage and shipping procedures will be provided in the laboratory investigator manual.

7.6.4. Sample Analysis

Plasma analysis will be performed via Platform Technology and Supply (PTS) - Third Party Resourcing (TPR), GlaxoSmithKline, the details of which will be included in the investigators manual. Concentrations of GSK3117391 and GSK3339189 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Plasma and urine samples collected for metabolite identification will be analysed for GSK3117391, GSK3339189 and other compound-related metabolites and the results reported under a separate PTS, GlaxoSmithKline protocol.

Concentration analysis in blood monocytes may be performed where samples allow. Analysis will be performed at a bioanalytical site under the control of PTS, IVIVT, GlaxoSmithKline, the details of which will be included in the Laboratory Investigator Manual. Concentrations of GSK3339189 will be determined using an approved

bioanalytical method. The raw data will be archived by the bioanalytical site, GlaxoSmithKline.

7.7. Pharmacodynamic Biomarkers

7.7.1. PD Biomarkers

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

- Levels of acetylation in monocyte and non monocyte cells in the blood.
- Blood samples will be analysed by flow cytometry for cell markers to determine any changes after treatment with GSK3117391.

7.7.2. RA disease biomarkers

7.7.2.1. Blood Biomarkers

Blood sample(s) will be collected during this study which may be used for the purposes of measuring biomarkers that are thought to influence RA. These may include but are not limited to:

- Serum C reactive protein
- Serum MRP8/14
- MMP1
- VCAM1
- Serum amyloid A

7.7.3. Novel biomarkers

Blood samples may be used for the purposes of measuring novel biomarkers that may influence disease/condition for study treatment, and/or medically related conditions, as well as the biological and clinical responses to GSK3117391. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Samples will be collected at the time points indicated in Section 7.1. 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.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with RA or medically related conditions and/or the action of GSK3117391 may be identified by application of:

- RNA transcriptomic analysis of blood samples.
- Measurement of the levels of a subset of RNA species in blood samples.
- Soluble cytokine and inflammatory mediators including, but not limited to, pro-inflammatory and anti-inflammatory cytokines, chemokines and acute phase proteins.

These may be reported separately after the clinical study report has been published. All samples may be retained for a maximum of 15 years after the last subject completes the trial.

7.8. Genetics

Subjects who do not wish to participate in the genetic research may still participate in the main clinical study. Information regarding genetic research is included in Appendix 5.

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.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA

9.1. Hypotheses

The study will evaluate the effect of GSK3117391 relative to placebo on the change from baseline in DAS28-CRP after 4 weeks of treatment. The primary analysis will test the null hypothesis of no treatment effect against the alternative hypothesis that there is a difference in DAS28-CRP change from baseline between the active and placebo groups.. This analysis will be fully documented in the Reporting and Analysis Plan (RAP).

9.2. Sample Size Considerations

Approximately 40 subjects will be randomised. Subjects will be randomised to either GSK3117391 or placebo with a 1:1 ratio.

9.2.1. Sample Size Assumptions

The study is not powered to detect pre-defined differences. For supportive information, with 20 subjects randomised to GSK3117391 and placebo groups respectively, the smallest difference in DAS28-CRP reduction between the two treatment groups at week 4 that would be statistically significant using a two sided test would be 0.6, assuming a standard deviation of 1.

9.2.2. Sample Size Sensitivity

The minimum detectable difference in DAS28-CRP reduction will be affected by changes from the assumed estimated standard deviation (SD) of 1. Table 5 below shows the effect of different estimates of the SD for the change from baseline in DAS28-CRP at week 4 on the minimum detectable difference.

Table 5 The effect of different assumptions for SD on the minimum detectable difference

Assumed standard deviation	Minimum detectable difference for change from baseline in DAS28-CRP at week 4
0.7	0.4
0.8	0.5
0.9	0.6
1	0.6
1.1	0.7
1.2	0.8
1.3	0.8

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be conducted.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations and Datasets

Safety Population: The 'Safety Population' is defined as subjects who receive at least one dose of study medication. This population will be used for the summary of all safety data.

Per-protocol population: The 'Per-protocol population' is defined as subjects in the 'Safety' population who are compliant with the dosing regimen (see Section 6.7) and that complete all protocol assessments and requirements. Analyses using the per-protocol population will include data from subjects who are compliant with the protocol up to the point that they are not compliant (for example if a subject withdraws on day 21 but is compliant until then, their data up to day 21 will be used). This population will be used for summary of efficacy, PD and biomarker data.

Pharmacokinetic population: The 'PK population' is defined as subjects in the 'Safety' population who received an active dose and for whom a pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only. In the

case of PK/PD, the Safety Population is used so that subjects receiving placebo can be included.

9.3.2. Interim Analysis

In line with routine pharmacovigilance, an internal GSK SRT which will include members of the 204957 study team, will review blinded safety data. In addition the DRC will review unblinded safety data (see Section 10.8 for further details) if necessary.

An unblinded interim analysis of the effect of GSK3117391 on monocyte counts will be conducted and reviewed by the DRC after approximately 10 subjects have completed the day 30 visit. This analysis may alter the timing of assessments in this or future studies. In addition to monocyte counts, other safety data may be reviewed and supporting data including pharmacokinetic and PD biomarkers may also be reviewed.

Unblinded interim analyses of efficacy will be conducted and reviewed by the DRC once appropriate numbers of subjects have completed the week 4 efficacy assessment, which may lead to a decision to stop the study for futility. In addition to efficacy data, safety data may be reviewed and supporting data including pharmacokinetic, PD biomarkers and RA disease biomarkers may also be reviewed.

A DRC charter will provide details of these reviews including timing, decision making and how the integrity of the study will be maintained (see Section 10.8 for further details of the DRC and Section 6.4 Blinding). Full details of the interim analyses will be pre-specified in the RAP.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The primary endpoint will be analysed using a Mixed effect Model for Repeated Measures (MMRM) adjusted for baseline DAS28-CRP score, treatment group, visit and the visit by treatment group interaction as fixed effects, patient as a random effect and visit within subject 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. The per-protocol population will be used for the primary analysis. Further sensitivity analyses may be conducted to assess the impact of missing data and nonparametric analyses may be conducted if the normality assumption does not hold.

9.4.2. Secondary Analyses

9.4.2.1. Safety Analyses

No formal statistical testing will be performed on safety data. All safety evaluations will be performed on the safety population. The safety data will be summarised descriptively and presented graphically. In addition, 95% credible intervals and probability statements

around the true event rate for specific AEs may be derived as appropriate to facilitate the interpretation of the safety data.

9.4.2.2. Secondary Efficacy Analyses

The primary endpoint (change in DAS28-CRP) will be analysed within a Bayesian framework using a repeated MMRM, adjusting for baseline DAS28-CRP score, treatment group, visit and the visit by treatment group interaction as fixed effects, patient as a random effect and visit within subject as a repeated effect.

Specific posterior probability statements around the true treatment difference in change from baseline in DAS28-CRP at week 4 and other timepoints as appropriate will be presented. For example, the probability that the true treatment difference in change from baseline in DAS28-CRP at week 4 is greater than 0.6 may be presented. Further details of the analysis including the definition of the prior distribution, will be specified in the RAP.

The proportion of subjects meeting ACR thresholds will be summarised using counts and proportions and analysed, if data allow, using a Generalised Estimating Equations (GEE) model adjusted for treatment group and baseline DAS28-CRP score. An estimate of the odds ratio of achieving the ACR threshold comparing GSK3117391 and placebo and associated p-values and 95% confidence intervals will be provided for week 4 and other timepoints as appropriate. All data will be summarised, graphically represented and listed appropriately.

9.4.2.3. Pharmacokinetic Analysis

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, GlaxoSmithKline. Blood samples will be collected to determine plasma concentrations of GSK3117391 and its acid GSK3339189. Plasma concentration-time data will be analysed by non-compartmental methods with Phoenix WinNonlin v.6.2.1 or greater. Calculations will be based on the actual sampling times recorded during the study. From the blood concentration-time data, the following pharmacokineticparameters will be determined, as data permit: maximum observed blood concentration(Cmax), time to Cmax (tmax), area under the blood concentration-time curve (AUC(0-t), AUC (0- τ), AUC(0-∞)), and apparent terminal phase half-life (t1/2). Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

The full pharmacokinetic profile for each subject will be reconstructed using Bayesian prediction from a population pharmacokinetic model using NONMEM version VII or higher and CL/F and V/F will be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. No statistical analysis of PK data will be carried out.

9.4.2.4. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory plots will be presented for individual plasma GSK3117391 (drug) and plasma and intracellular GSK3339189 (acid) concentrations versus selected markers of clinical efficacy (including DAS28-CRP) and exploratory endpoints (including but not limited to selected blood cell quantification, acetylation of selected blood cells, soluble cytokine and inflammatory mediators, CRP and MRP8/14 expression). Additional exploratory plots will be presented of selected derived PK parameters from plasma levels of GSK3117391 and plasma / intracellular levels of GSK3339189 versus selected markers of clinical efficacy (e.g DAS28-CRP at week 4) and exploratory endpoints.

If data permit, further PK/PD modelling will be performed based on the results of the exploratory graphical analysis showing obvious relationships or trends between plasma concentration and the pharmacodynamic parameters. The choice of the structural pharmacokinetic/pharmacodynamic model will be dependent on the emerging data. More details of any exploratory pharmacokinetic/pharmacodynamic analysis will be provided in the RAP.

9.4.3. Other Analyses

All exploratory endpoints will be summarised descriptively, graphically presented and statistically analysed if deemed appropriate. Further details will be specified in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

Prior to initiation of a site, GSK will obtain 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.
- 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 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 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) agree 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 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, archiving 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 randomisation codes for their site only after completion of the full statistical analysis.

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

10.8. Review Committees

10.8.1. Safety Review Team

Instream review of blinded individual level safety data including AE, SAEs, vital signs and laboratory data (with the exception of monocyte counts which will be summarised only, see Section 6.4) will be conducted by a Safety Review Team (SRT) during study conduct. The membership of the SRT (including members of the central GSK study team) and the proposed frequency of review is documented in the SRT charter.

10.8.2. Data Review Committee

Interim analyses of unblinded data will be conducted to assess the effect of GSK3117391 on monocyte count, and for futility. The DRC may also perform an interim analysis on safety data if the SRT feels that this is warranted. These results will be reviewed by the internal DRC (see Section 9.3.2). No members of the study team involved in the direct day to day conduct of the study or in the acquisition of data will take part in the DRC In addition, in order to protect the interests of subjects and ensure their safety, the DRC will include one or more members of GSK's Global Safety Board who are not members of the study team. The membership and timing of the planned interim analyses and the decision making framework for DRC reviews are described in the DRC charter. The analysis plan for DRC reviews are described in the RAP. All available data may be reviewed by the DRC.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

°C	Degree Celsius
µg	Microgram
ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ACR20/50/70	20%/50%/70% improvement in tender and swollen joint counts and 20%/50%/70% improvement in 3 of the 5 ACR-core set measures
AE	Adverse event
ALT	Alanine transaminase
AMD	Age-related macular degeneration
AST	Aspartate transaminase
AUC	Area under the curve
AUC0-∞	Area under plasma (serum) concentration-versus-time curve (time zero to infinity)
AUC0-t	Area under the plasma (serum) concentration-versus-time curve (time zero to time of last quantifiable concentration)
BUN	Blood Urea Nitrogen
hCG	Human chorionic gonadotropin
CPK	Creatine phosphokinase
CRP	C-reactive protein
CYP	Cytochrome P
DAS28-CRP	Disease activity score for 28 different joints with CRP value
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DMARD	Disease modifying anti rheumatic drug
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ESM	Esterase Sensitive Motif
EULAR	European League Against Rheumatism
FRP	Females of reproductive potential
FSH	Follicle-stimulating hormone
FTIH	First time in human
g	Gram
GSK	GlaxoSmithKline
h	Hour
hCE-1	Human carboxy-esterase-1
HAQ-DI	Health Assessment Questionnaire Disability Index
HDAC	Histone deacetylase
HIV	Human Immunodeficiency Virus

HRT	Hormone replacement therapy
IA	Intra-articular
IB	Investigator brochure
IC50	The half maximal inhibitory concentration
ICH	International Conference on Harmonization
IM	Intramuscular
INR	International normalised ratio
IP	Investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRTS	Interactive response technology system
IU	International units
IV	Intravenous
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical dictionary for regulatory activities
MET ID	Metabolite Identification
mg	Milligram
mL	Milliliter
MMRM	Mixed effect Model for Repeated Measures
MRP	Myeloid-related protein
MSDS	Material safety data sheet
MTX	Methotrexate
ng	Nanogram
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
PtGA	Patient's Global Assessment of Arthritis
PtAAP	Patient's Assessment of Arthritis Pain
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetics
PTS	Platform Technology and Supply
RA	Rheumatoid arthritis
RAP	Reporting and analysis plan
RF	Rheumatoid Factor
SAE	Serious adverse event
SD	Standard Deviation
SJC	Swollen Joint Count
SOP	Standard operating procedure
SRM	Study Reference Manual
SRT	Safety Review Team
t½	Elimination half-life
TB	Mycobacterium tuberculosis

TJC	Tender Joint Count
TNFα	Tumor necrosis factor alpha
TPR	Third Party Resourcing
VAS	Visual Analogue Scale

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Eanercept
Humira
Prosorba
QuantiFERON-TB
Remicade
Simponi
WinNonlin

12.2. Appendix 2: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.2.1. 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.

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

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

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable).

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 91 days after the last dose of study medication.

1. Male condom plus recommendation for partner use of one of the contraceptive options below that meets the Standard operating procedure (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.

In addition, male subjects are prohibited from donating sperm until 91 days after the last dose of study medication.

12.2.2. Collection of Pregnancy Information

- 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 foetal 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. 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.
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomised to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy.

- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

12.2.3. References

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12.3. Appendix 3: 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.

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• 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, stabilise, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment

MONITORING:</td><td colspan="2">• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours after last dose, per protocol where possible[5]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter</td></tr>
</table>

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

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

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 normalise or return to within baseline.

References

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

12.4. Appendix 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 (haematology, 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

Events NOT meeting definition of an AE include:
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., hospitalisation 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 hospitalisation or prolongation of existing hospitalisation NOTE: • In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation 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 hospitalisation but may jeopardise 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 hospitalisation, 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
- Revascularisation

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 utilised 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 recognised 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 SAE coordinator.
- 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 SAE coordinator 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: 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 GSK3117391 or any concomitant medicines.
- RA 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 utilise 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 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 randomised 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 utilise 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 analysed during the study or stored for future analysis.

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

Screen 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. However, if patient is re-screened successfully then the original genetic sample will be kept to avoid re-sampling.

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

GSK may summarise 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. Furthermore, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.6. Appendix 6: Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7: Protocol Changes

This is the third Amendment to Protocol 204957 (2016-DEC-08). This amendment is applicable to all countries and sites participating in study 204957.

The changes in this amendment are to provide clarity regarding extension to the screening window and other study requirements throughout the protocol.

Changes in this amendment:

Section of protocol	Original text	Text in amendment
4.1 Overall Design	No footnote for Figure 1	The screening window can be extended for up to 56 days to allow only for the washout of background DMARD therapy if necessary (footnote added)
4.1.1 Screening	Subjects will be screened up to 28 days prior to the Day 1 visit (randomisation and start of the treatment period).	All subjects must provide written informed consent for the study prior to the start of screening period. Subjects will be screened up to 28 days prior to the Day 1 visit (randomisation and start of the treatment period). The screening window can be extended for up to 56 days to allow only for the washout of background DMARD therapy if necessary (see Section 6.11.2 for washout periods for DMARD therapies and other medications). Subjects on medications requiring longer washout than 56 days prior to Day 1 must have discontinued medication for the stated washout time in Section 6.11.2 before being considered for eligibility in this study. All other screening assessments must be performed within 28 days prior to Day 1(dosing Day 1).

Section of protocol	**Original text**	**Text in amendment**
4.3. Type and Number of Subjects	Approximately 80 subjects with RA will be screened, from these approximately 40 will proceed to randomisation. This assumes a screen fail rate of up to 50% and a dropout rate of approximately 15%.	Approximately 40 subjects will be randomised. This assumes a dropout rate of approximately 15%.
4.4. Design Justification	If a subject experiences an unacceptable level of disease activity during the study, the investigator may withdraw the subject at any point.	If a subject experiences an unacceptable level of disease activity during the study, the investigator may withdraw the subject from further study treatment at any point. The subject is then to enter the follow up period, where subject will be able to receive standard of care treatment at the discretion of the investigator as early as 7 days after the last dose of study medication.
5.1. Inclusion Criteria Type Of Subject And Diagnosis Including Disease Severity	The subject must have a diagnosis of RA according to the 2010 ACR/EULAR classification criteria for RA.	The subject must have a diagnosis of RA as an adult (≥18 years) according to the 2010 ACR/EULAR classification criteria for RA.
5.1. Inclusion Criteria Sex, female	A negative hCG pregnancy test, (serum at screening visit and urine for subsequent visits, with a sensitivity of at least 25 IU/L) is required at the screening visit, between Day-7 to -4 and on Day 1 prior to dose administration. Further pregnancy tests are required at the weekly study visits and the follow-up visit.	A negative serum hCG pregnancy test at the first screening visit and urine hCG pregnancy test (with a sensitivity of at least 25 IU/L) at the following visits: between Day-7 to -4, on Day 1 prior to first study medication dose administration, at the weekly study visits, and the follow up visit.
5.1. Inclusion Criteria	The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.	The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception and receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures.

Section of protocol	**Original text**	**Text in amendment**
5.2. Exclusion Criteria Concurrent Conditions/Medical History (Includes Liver Function And QTc Interval) #3	Subjects who have previously been treated with more than 1 biologic agent (such as TNF inhibitors eg. adalimumab, etanercept, infliximab, certolizumab, golimumab or non-TNF inhibitors eg.abatacept, rituximab, tociluzimab) or any investigational biologic.	Subjects who have previously been treated with more than 1 biologic agent (such as TNF inhibitors and their biosimilars eg. adalimumab, etanercept, infliximab, certolizumab, golimumab or non-TNF inhibitors and their biosimilars eg.abatacept, rituximab, tociluzimab) or any investigational biologic.
5.2. Exclusion Criteria Concurrent Conditions/Medical History (Includes Liver Function And QTc Interval) #7	Inclusion 7 as in original text	Each parameter unit power is superscripted for ease of the reader
5.3.1. Rescreening	If a subject has not met all of the Eligibility Criteria within the screening period, rescreening is permitted. Subjects are only allowed to be re-screened once; the entire screening process must be repeated.	Re-screening is permitted with the approval of the medical monitor if a subject has not met the Eligibility Criteria within the screening period with the following exception: • If a subject fails screening due to Exclusion Criteria 6 and/or 7 in Section 5.2, rescreening is not permitted. Subjects are only allowed to be re-screened once; the entire screening process must be repeated. Chest X-ray does not need to be repeated during re-screening, if one was conducted within 12 weeks of re-screening Day 1 and showed no evidence of current or previous pulmonary tuberculosis, locally read by a radiologist. Repeat testing of glucose-6-phosphate dehydrogenase (G6PD) deficiency during rescreening is not needed, if test result during original screening was negative.

Section of protocol	Original text	Text in amendment
5.3.2.1. Laboratory tests	If a subject fails any of the laboratory exclusion criteria, the test may be repeated twice within the screening period. If the subject fails the laboratory criteria for a third time they will be considered a screen failure; these subjects may be re-screened as described in Section 5.3.1. If a blood sample has to be redrawn due to sample handling problems, breakage or sample integrity, this is not considered a re-test.	If the investigator is not able to assess subject's eligibility for any of the laboratory exclusion criteria in cases of (a) technical malfunction (e.g. loss of laboratory specimen); (b) an indeterminate result or (c) if there is reason to believe the result may be false (i.e. contradicts recent result for the same parameter) the test may be repeated once within the screening period after consultation with the medical monitor. If the original result was exclusionary and is confirmed by repeat testing then the subject is to be considered a screen failure; these subjects may be re-screened as described in Section 5.3.1.
6.1. Investigational Product and Other Study Treatment	No original text	Store refrigerated (2 – 8°C) (row added for study treatment)
6.4. Blinding	The anticipated effect of GSK3117391 on monocyte count may unblind a subject's treatment allocation to any reviewer. As a consequence, monocyte count data (which will be analysed in a central laboratory) will not be available to the site during the study. Investigators will be able to view blinded WBC counts. Summary monocyte counts for all subjects will be reviewed by the SRT; however, individual level monocyte count data will only be reviewed by the DRC.	The anticipated effect of GSK3117391 on monocyte count and CRP may unblind a subject's treatment allocation to any reviewer. As a consequence, monocyte count data and CRP (both of which will be analysed in a central laboratory) will not be available to the site during the study after screening. Investigators will, therefore, be blinded to the monoctye count but will be able to view other WBC counts. Summary monocyte counts for all subjects will be reviewed by the SRT once sufficient subjects have been recruited to avoid unblinding. Individual level monocyte count and CRP data will only be reviewed by the DRC.

Section of protocol	**Original text**	**Text in amendment**
6.6. Preparation/Handling/Storage/Accountability	No special preparation of study treatment is required.	No special preparation of study treatment is required. The study treatment must be stored refrigerated (2-8^{o}C) at site, and at subject's home.
6.7. Compliance with Study Treatment Administration	Only subjects with appropriate compliance will be included in the per-protocol dataset for the primary analysis.	Only subjects with appropriate compliance will be included in the per-protocol population for the primary analysis.
6.8. Treatment of Study Treatment Overdose	For this study, any dose of GSK3117391 > 80mg (ie >4 capsules) within a 26 hour time period will be considered an overdose.	For this study, more than 4 capsules of the study medication within a 26 hour time period will be considered an overdose.
6.11.1. Permitted Medications and Non-Drug Therapies	First paragraph removed	Inserted in Section 6.11. Concomitant Medications and Non-Drug Therapies
6.11.1.2. NSAIDs	Continued use of NSAIDs is permitted (i.e. diclofenac, ibuprofen, ketoprofen, naproxen etc) in daily doses up to the maximum recommended according to locally accepted clinical practices if the dosage was stable for at least 2 weeks before screening.	Continued use of NSAIDs is permitted (i.e. diclofenac, ibuprofen, ketoprofen, naproxen, celecoxib and etoricoxib etc) in daily doses up to the maximum recommended according to locally accepted clinical practices if the dosage was stable for at least 2 weeks before screening. The concomitant use of proton pump inhibitors, e.g. omeprazole or pantoprazole, is strongly recommended in order to lower the risk of complications affecting the gastrointestinal tract caused by NSAIDs.
6.11.2. Prohibited Medications and Non-Drug Therapies	Table 1: Prohibited throughout the study, from the time periods stated until the follow up clinic visit: For subjects on medications requiring washout of >28 days (see below), written informed consent for the study must be	Table 1: Prohibited throughout the study, from the time periods stated until after 7 days from the last dose of the study medication: (paragraph deleted)

Section of protocol	Original text	Text in amendment
	obtained prior to beginning the screening period. However, other screening assessments, other than consent, must occur within 28 days prior to randomisation Any conventional DMARDs No original text Tofacitinib	Any conventional DMARDs (if not listed here please contact medical monitor) 26 weeks prior to Day 1 washout for Gold salts (row added) Tofacitinib Baricitinib
7. Study Assessments And Procedures	If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:	If assessments are scheduled for the same nominal time, then the assessments should, where possible, occur in the following order:
7.1. Time and Events Tables Table 2: Screening and Follow-up Assessments	**Notes:** No original text EW = Early Withdrawal Informed consent must be obtained prior to any study procedures being conducted. Screening is serum pregnancy test, all subsequent testing urine. An additional pregnancy test is required 4-7 days prior to Day 1. FRP only. No original text	1. Screening period can be extended to 56 days to allow ONLY the washout of background DMARD therapy where necessary. All other assessments must be completed within 28 days prior to Day 1. Some assessment can occur on separate visit 2. For EW = (Early Withdrawal) visit, assessments are to be conducted as deemed necessary based on PI's judgment and to be recorded as a unscheduled visit in the subject's CRF Informed consent must be obtained prior to any study procedures being conducted including DMARD therapy washout period. First test in screening is serum pregnancy test, all subsequent testing urine. An additional pregnancy test during screening visit (urine) is required 4-7 days prior to Day 1. FRP only. Contraception use compliance (row added)

Section of protocol	**Original text**	**Text in amendment**
	aCCP CRP	ACPA hs-CRP (reordering of few assessments)
7.1. Time and Events Tables Table 3: Day 1 to Day 30 On-Study Assessments	No original text aCCP CRP Time in relation to dose (no footnote) D2, 28 & D30 (no footnote) RA disease biomarker sampling Isolated monocyte PK (no footnote)	Contraception use compliance (row added) ACPA hs-CRP Sample collection and assessments to be conducted in accordance with the time and events table (footnote added) Blood samples to be collected within a ± 1 h window of the schedule time(footnote added) Sample will be collected and stored for future analysis. (footnote added) Applicable to selected sites only (footnote added) Abbreviations added, reordering of few assessment
7.2. Screening and Critical Baseline Assessments	ACR response HAQ-DI No original text Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified. No original text	ACR criteria HAQ-DI which includes an item on pain severity during the past week Patient reported outcome (subheading added) Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified above. The investigator is responsible for ensuring that subjects understand how to properly use contraception methods detailed in Appendix 2 and receive continued guidance during screening and study conduct with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the followings: • Contraceptive requirements of the study

Section of protocol	Original text	Text in amendment
		• Assessment of subject compliance through questions such as • Have you forgotten to use contraception since the last visit? • Is there a chance you could be pregnant? (section rearranged for consistency)
7.3. Efficacy	Efficacy assessments will include evaluation of all 68 joints for tenderness and 66 joints for swelling to be performed by an independent joint evaluator, Visual Analogue Scale (VAS) for global disease for the subject and treating physician, health assessment questionnaire – disability index (HAQ-DI – physical function, which includes an item on pain severity in the past week), and laboratory assessments (CRP). Based on these assessments ACR (20, 50 and 70), DAS28-CRP and the EULAR response will be calculated.	Efficacy assessments will include Health Assessment Questionnaire – Disability Index (HAQ-DI – physical function,), Patient's assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, evaluation of all 68 joints for tenderness and 66 joints for swelling (to be performed by an independent joint evaluator), Physician's Global Assessment of Arthritis and laboratory assessments (including CRP). Based on these assessments ACR (20, 50 and 70), DAS28-CRP and the EULAR response will be calculated by the central GSK team.
7.4.1.	DAS measurements Sites/investigators will not have access to ongoing DAS scores	DAS28 measurements Sites/investigators will not have access to ongoing DAS28 scores
7.4.2. ACR measurements	Health Assessment Questionnaire – Disability Index (HAQ-DI)	Health Assessment Questionnaire – Disability Index (HAQ-DI) which includes an item on pain severity during the past week. (section rearranged for consistency)
7.5.6. Clinical Safety Laboratory Assessments	No original text	Investigators should note that due to the anticipated effect of GSK3117391 on monocyte count, any local WBC panel assessments may unblind a subject's treatment allocation to any reviewer. Therefore, every effort should be made to ensure that local monocyte count data is not available to the site

Section of protocol	**Original text**	**Text in amendment**
		during the study. Investigators will however be able to view total WBC counts and differential WBC counts that do not include monocyte counts. (paragraph added)
Table 4: Protocol Required Safety Laboratory Assessments	aCCP	ACPA Central laboratory serum pregnancy test for the first visit during screening.(sentence added to Note #2)
7.6.3. Monocyte isolation	Processing, storage and shipping procedures are provided in the laboratory investigator manual.	Processing, storage and shipping procedures will be provided in the laboratory investigator manual.
7.7.1. PD Biomarkers	Soluble biomarkers in the blood which may be predictive of response to GSK3117391 such as IL-6.	Sentence deleted
9.2. Sample Size Considerations	Approximately 80 subjects will be screened and approximately 40 randomised. Subjects will be randomised to either GSK3117391 or placebo with a 1:1 ratio.	Approximately 40 subjects will be randomised. Subjects will be randomised to either GSK3117391 or placebo with a 1:1 ratio.
9.3.1. Analysis Populations and Datasets	Per-protocol dataset	Per-protocol population (replaced throughout)
12.5. Appendix 5: Genetic Research	“Screen failures” section	However, if patient is re-screened successfully then the original genetic sample will be kept to avoid re-sampling.(sentence added)

Changes in amendment 2:

Section of protocol	**Original text**	**Text in amendment**
4.4 Design justification	The study is sponsor open to enable members of the Data Review Committee (DRC) to be unblinded for the planned interim analyses of monocyte counts	The study is sponsor open to enable members of the Data Review Committee (DRC) to be unblinded for the planned interim analyses of safety data (including clinical laboratory parameters and AEs), monocyte counts
5.4.2 Group safety stopping criteria	AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subjects will be regularly reviewed by the Sponsor Safety Review Team (SRT) and/or the iSRC in order to ensure appropriate subject safety.	AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subjects will be regularly reviewed by the Sponsor Safety Review Team (SRT) and/or the DRC in order to ensure appropriate subject safety.
6.4 Blinding	However, monocyte data will be reviewed with other data by the iSRC an maybe reviewed by the DRC	Summary monocyte counts for all subjects will be reviewed by the SRT however, individual level monocyte count data will only be reviewed by the DRC.
7.1 Time and events tables	HIV, Hep B and Hep C screen, TB,	HIV, Hep B and Hep C screen, TB, G6PD
7.1 Time and events tables	PK blood sample	PK blood sample and MetID

Section of protocol	**Original text**	**Text in amendment**
9.3.2 Interim analysis	In addition an iSRC will review unblinded safety data (see Section 10.8 for further details) .	In addition the DRC will review unblinded safety data (see Section 10.8 for further details) if necessary.
9.3.2 Interim analysis	other safety data will be reviewed	other safety data may be reviewed
9.3.2 Interim analysis	An unblinded interim analysis of efficacy will be conducted and reviewed by the DRC once appropriate numbers of subjects have completed the week 4 efficacy assessment, which may lead to a decision to stop the study for lack of efficacy. In addition to efficacy data, safety data will be reviewed	Unblinded interim analyses of efficacy will be conducted and reviewed by the DRC once appropriate numbers of subjects have completed the week 4 efficacy assessment, which may lead to a decision to stop the study for futility. In addition to efficacy data, safety data may be reviewed
10.8.1 Safety review team	Instream review of blinded safety data including AE, SAEs, vital signs and laboratory data (with the exception of monocyte counts, see Section 6.4)	Instream review of blinded individual level safety data including AE, SAEs, vital signs and laboratory data (with the exception of monocyte counts which will be summarised only, see Section 6.4)
10.8.2 Internal safety review committee	An Internal Safety Review Committee (iSRC) will be utilised in this study and comprise individuals who are not members of the clinical study team. The iSRC is positioned to offer an internal, independent review of safety data (and other data types when required) to protect the interests of subjects and ensure their safety. All efforts will be made to maintain the study integrity and validity of study data. The schedule of planned reviews of safety data and the analysis plan for iSRC review is described in the iSRC Charter.	Whole section removed

Section of protocol	Original text	Text in amendment
10.8.3 Data review committee		The DRC may also perform an interim analysis on safety data if the SRT feel that this is warranted. (sentence added)
10.8.3 Data review committee		In addition, members of the global safety board who are not members of the study team will perform an independent review of safety data when reviewed to protect the interests of subjects and ensure their safety. (sentence added)

Changes in amendment 1:

Section of protocol	Original text	Text in amendment
Section 4.1, Figures 1	study schematic: outpatient visit on day 15	outpatient visit on day 14
Section 5.1, Inclusion criteria 10	A female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test),	A female subject is eligible to participate if she is not pregnant (as confirmed by a negative human chorionic gonadotrophin (hCG) test),
Section 5.1, Inclusion criteria 10b	A negative pregnancy test (serum or urine hCG pregnancy test with a sensitivity of at least 25 IU/L) is required on Days -28, Day-7 to -4 and Day 1	A negative hCG pregnancy test, (serum at screening visit and urine for subsequent visits, with a sensitivity of at least 25 IU/L) is required at the screening visit, between Day-7 to -4 and on Day 1
Section 5.2 Exclusion criteria 28	'No evidence of active or latent infection'	Evidence of active or latent infection'

Section of protocol	**Original text**	**Text in amendment**
Section 6.11.2	'For subjects on medications requiring washout of >28 days (see above'	'For subjects on medications requiring washout of >28 days (see below)'
Section 6.11.2 Table 1	'atazanvir' 'volconazole'	'atazanavir' 'voriconazole'
Section 7.1, Table 2	On table 2, no foot note next to 'outpatient visit'	Footnote added 'Additional screening visit needed for FRP pregnancy test 4 to 7 days pre day 1'
Section 7.1, Table 2	'Haem/Chem/Urinalysis tests'	Footnote added to 'Haem/Chem/Urinalysis tests' 'Including INR/APTT (coagulation) and MetHb (MetHb, performed locally)'
Section 7.1, Table 2	'PD biomarker sample'	Footnote added to: 'PD biomarker sample' 'This includes biomarkers for RA disease and exploratory PD, acetylation'
Section 7.1, Table 2	'Chest xray'	Footnote added to 'Chest xray' 'Only required at screening if no CXR performed within 12 weeks of Day 1 visit'
Section 7.1, Table 2	'gene expression blood' missing from table	Row added 'Gene expression blood' with 'x' in follow up visit column
Section 7.1, Table 3	clinical chemistry/urinalysis	'x' to indicate additional assessments at day 7, 14 and 21 visit
Section 7.1, Table 3	Coagulation	Coagulation (INR/IPTT)'
Section 7.1, Table 3	Joint counts: TJC (68), SJC (66)	'x' to indicate assessment required at day 28

Section of protocol	**Original text**	**Text in amendment**
Section 7.1, Table 3	(MetHb missing from table)	Row added 'MetHb' with 'x' in columns day 14 and day 28
Section 7.1, Table 3	'Monocyte PK blood'	'Isolated monocyte PK'
Section 7.1, table 3	'gene expression blood'	'x' to indicate assessment at day 28 removed
Section 7.6.6, Table 4	Table 4 missing Note 3	Note added ' 3 The following parameters will only be performed at selected time points as per Time and Events Table: INR, MetHb, CRP'
Section 7.8.3	GS3117391	GSK3117391