TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with moderate to severe rheumatoid arthritis.

Compound Number: GSK2982772

Development Phase: II

Effective Date: 20-APR-2017

Protocol Amendment Number: 03

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N251670_00	2016-APR-01	Original
2015N251670_01	2016-MAY-25	Amendment No. 1
Protocol Amendment 01 incorporates the addition of risk text for drug interaction with P-glycoprotein (Pgp) inhibitors and narrow therapeutic index (NTI) CYP3A4 substrates, an updated list of prohibited medications plus some minor protocol clarifications and administrative changes.		
2015N251670_02	2016-JUL-14	Amendment No. 2
Protocol Amendment 02 incorporates addition of suicidal ideation and behaviour (SIB) withdrawal criteria plus other minor protocol clarifications and administrative changes.		
2015N251670_03	2017-APR-20	Amendment No. 3
Change in dosing regimen from 60 mg BID to 60 mg TID, restrictions on JAK inhibitors, defined non-reproductive potential criteria in Exclusion 11, change to clinical laboratory criteria in Exclusion 23, addition of evaluation of joint space narrowing with MRI, flexibility in scheduling with MRI and synovial biopsy, some minor protocol clarifications and administrative changes.		

SPONSOR SIGNATORY

PPD

20th April 2017

Caroline Savage, PPD MD
Vice President & Head Experimental Medicine Unit
Immunoinflammation Therapy Area

Date

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(s): EudraCT 2016-000912-13

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 203168

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 203168

Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with moderate to severe rheumatoid arthritis (RA) who are currently being treated with disease modifying anti-rheumatic drugs (DMARDs).

The primary objective of this study has not changed with amendment 03; however the dosing regimen does change to GSK2982772 (60 mg three times daily for 84 days).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg three times daily for 84 days). In addition to the pharmacokinetics (PK), a number of experimental and clinical endpoints will be employed to obtain information on the pharmacodynamics (PD), and preliminary efficacy in subjects with active RA. Although no formal hypothesis will be tested, these endpoints will enable a broader understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in RA, by making full use of the information obtained from each subject enrolled.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8 and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).

Objectives	Endpoints

• To investigate the effect of 60 mg three times daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Magnetic Resonance Imaging (MRI) parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, bone oedema and joint space narrowing as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, the RAMRIQ (Rheumatoid arthritis MRI quantitative) scoring system, the modified CARLOS (Cartilage Loss Scoring System) and additional exploratory endpoints as data permit.
	• Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:
	  • Exchange rate (K^{trans})
	  • Interstitial volume (V_e)
	  • Plasma volume (V_p)
	  • Initial rate of enhancement (IRE)
	  • Maximal signal intensity enhancement (ME)
	  • Joint volume
	  • Enhancing volume

• To investigate the effect of 60 mg three times daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg three times daily dosing of GSK2982772 on methotrexate (MTX) concentrations.	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue from subjects with moderate to	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells,

Objectives	Endpoints
severe Rheumatoid Arthritis.	and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.
• To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and synovial biopsy tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit: • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue. • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg three times daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood subjects with active moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA. The study design schematic is depicted in Figure 1 below.

Figure 1 Study Overview

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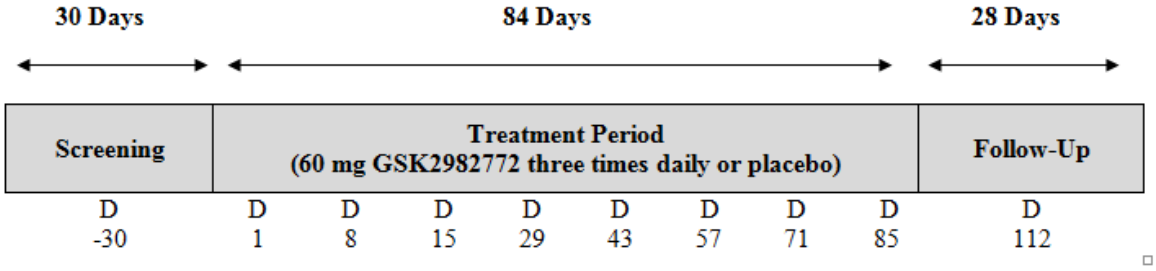

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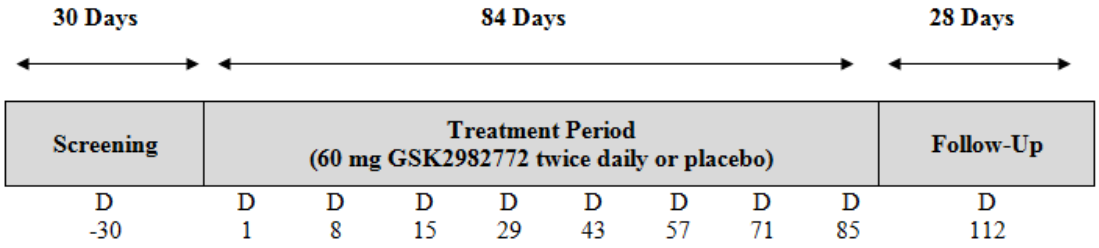

Key assessments:
Safety assessments, PK samples, DAS28-CRP, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom and Impact Diary, HAQ-DI assessments, MRI, PD samples

Treatment Arms and Duration

Each subject will participate in the study for approximately 20 weeks. This includes a screening period of up to 30 days, an 84 day (12 week) treatment period, and a 28 day follow-up period after the last dose.

Within 30 days of the screening visit (defined as day of consent signing), subjects who are eligible will enter the treatment period and start treatment (or dosing) on Day 1.

The Follow-up Period is 28 days (4 weeks) long. All visits and assessments are detailed in Section 7.1.

Subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg three times daily (TID)

Placebo three times daily (TID)

Prior to amendment 03 being effective in each country, subjects have been randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg two times daily (BID)

Placebo two times daily (BID)

Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 24 subjects with moderate to severe RA are randomised into the study on a TID regimen. Prior to protocol amendment 03 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Should the overall drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to an overall total maximum of 48) into the study at the discretion of the Sponsor.

Analysis

The safety and tolerability of GSK2982772 following 12 weeks of treatment will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead electrocardiogram (ECG) monitoring.

Ongoing reviews of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GlaxoSmithKline (GSK) individuals, some of who are also members of the GSK study team who are not involved with the day-to-day running of the study. The primary purpose of these reviews will be to monitor target engagement, inflammatory markers and Disease activity score for 28 different joints with (CRP) value (DAS28-CRP) for futility and internal decision making. A data review charter will outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted during the study, when an appropriate number of subjects have completed 12 weeks of treatment or on the request of the DRC. The purpose of this interim will be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in DAS28-CRP

will be statistically analysed using a Mixed-effect Model Repeat Measurements (MMRM) comparing GSK2982772 with placebo at each time point.

The relationship between each of the mechanistic endpoints and also with the clinical endpoints may also be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g DAS28-CRP). In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain change in DAS28-CRP (i.e., comparatory rate), based on the data that we have observed in the study. Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

2. INTRODUCTION

2.1. Study Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with moderate to severe rheumatoid arthritis (RA) who are currently being treated with disease modifying anti-rheumatic drugs (DMARDs). All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication type and dose is stable throughout the study.

The primary objective of this study has not changed with amendment 03; however the dosing regimen does change to GSK2982772 (60 mg three times daily for 84 days).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg three times daily for 84 days). In addition, a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy in subjects with moderate to severe RA.

2.2. Brief Background

RIP1 is a member of the receptor-interacting Serine/Threonine kinase family containing an amino-terminal kinase domain, an intermediate domain and a carboxy-terminal death domain. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including tumor necrosis factor (TNF) family cytokines, ligands for toll-like receptor (TLR) 3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis

[Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008, Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_02]. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and NF-kB-signalling [Ofengeim, 2013, Humphries, 2015]. With this, an inhibitor of RIP1 kinase activity with GSK2982772 may fill a unique niche in the treatment of inflammatory conditions through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a debilitating, progressive polyarthritis that typically affects the small joints of the hands and feet [Vasanthi, 2007]. TNF is known to be one of the key cytokines that drives inflammation in RA [Choy, 2001]. In animal models, transgenic mice that chronically over express low levels of TNF develop a spontaneous polyarthritis that resembles RA in humans [Keffer, 1991] and blockade of NFκB activation results in the development of a spontaneous murine polyarthritis that is RIP1-dependent [Berger, 2014]. In RA patients, TNF is detected in high concentrations in both blood and synovial fluid, and expression of TNF and its signalling intermediates, including RIP1, have been shown to be constitutively increased in PBMCs from RA subjects compared to healthy controls [Raghav, 2006].

Synthetic disease modifying antirheumatic drugs (DMARDs) including nonsteroidal anti-inflammatory drugs, steroids, methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide, are often used alone or in combination in moderate to severe RA; however, most DMARDs do not significantly impact disease progression, and may be hampered by poor side effect profiles. Recently, tofacitinib, an oral small molecule inhibitor of JAK, was approved for moderate to severe RA, but its long term safety is still unknown. TNF antagonists are used in the treatment of patients with moderate-severe disease who have not responded or who have intolerance to traditional DMARDs. While studies have shown that they can improve symptoms and slow the progression of joint damage in many patients [Agarwal, 2011], only half of RA patients achieve American College of Rheumatology (ACR) 50 criteria, and many become refractory to anti-TNF treatments after several years. In addition to the association with increased rates of opportunistic infections across all indications, anti-TNF therapy in RA is linked to lupus-like syndrome and increased rates of demyelinating disease. Other biologic therapies which inhibit T cell activation (abatacept) or lead to selective B cell depletion (rituximab) have shown clinical efficacy in anti-TNF refractory patients, although both carry potential risks for serious infection. Therefore, there remains a high unmet need for safe and tolerable therapies that lead to improved rates of clinical remission and increased physical function in patients with moderate to severe RA.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8, and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in MRI parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, bone oedema and joint space narrowing as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, the RAMRIQ (rheumatoid arthritis MRI quantitative) scoring system, the modified CARLOS (Cartilage Loss Scoring System) and additional exploratory endpoints as data permit. • Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:

Objectives	Endpoints
	• Exchange rate (K^{trans}) • Interstitial volume (V_e) • Plasma volume (V_p) • Initial rate of enhancement (IRE) • Maximal signal intensity enhancement (ME) • Joint volume • Enhancing volume
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg three times daily dosing of GSK2982772 on methotrexate (MTX) concentrations	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.

• To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit:
	  • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue.
	  • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.

Objectives	Endpoints
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg three times daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

4. STUDY DESIGN

4.1. Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA. The study design schematic is depicted in Figure 2 below.

Figure 2 Study Overview

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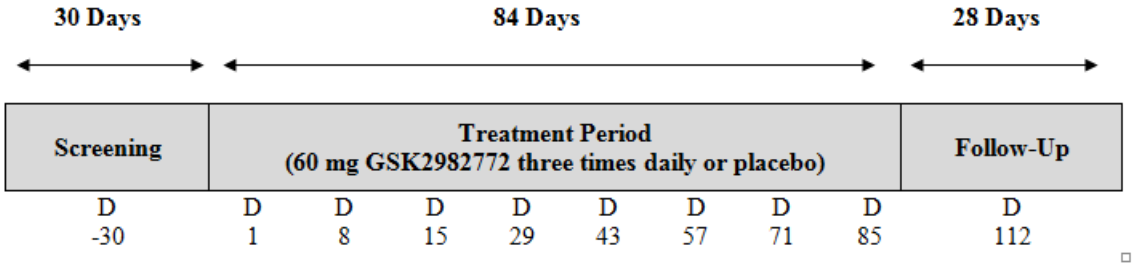

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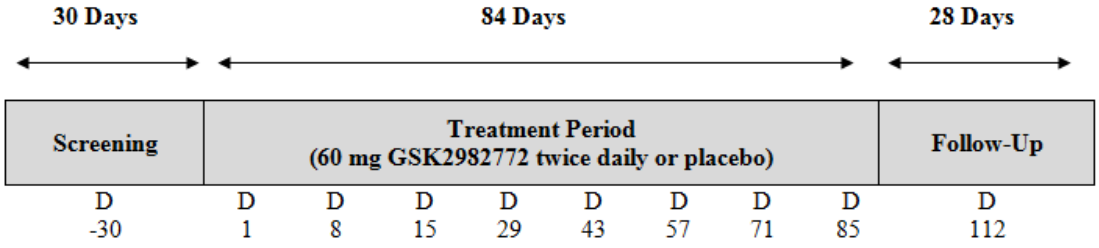


Key assessments:
Safety assessments, PK samples, DAS28-CRP, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom and Impact Diary, HAQ-DI assessments, MRI, PD samples

4.2. Treatment Arms and Duration

It is anticipated that the total duration of participation in the study will be approximately 20 weeks from screening to the last study visit.

4.2.1. Screening

Within 30 days of the screening visit (defined as day of consent signing), subjects who are eligible will enter the treatment period and start treatment (or dosing) on Day 1.

4.2.2. Treatment Period

Subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally three times daily (approximately 8 hours apart) for 84 days (12 weeks). Subjects that were randomised prior to protocol amendment 03 being approved in each country were randomly assigned to either GSK2982772 60 mg or placebo orally two times daily (approximately 12 hours apart) for 84 days (12 weeks).

Further guidance and information for study treatment and dosing are provided in the Study Reference Manual (SRM).

During the 84 day (12 week) treatment period, subjects will attend the clinical site for visits on Days 1, 8, 15, 29, 43, 57, 71 and 85. At specific visits, subjects must not take study treatment prior to their scheduled visit (see Section 7.1). On Days 22, 36, 50, 64 and 78, each subject will be contacted by telephone and asked about their general health, study medication compliance and diary card completion. Subjects will be given a diary card at each of the visits on which they will be instructed to record their daily study medication and concomitant medication taken and any adverse events.

4.2.3. Follow-up Period

After the Treatment Period, the subject will enter the Follow-up Period which lasts for 28 days post the last administration of study medication, in order to complete follow-up assessments per the Time and Events Table (see Section 7.1).

4.3. Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 24 subjects with moderate to severe RA are randomised into the study on a TID regimen. Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Should the overall drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to an overall maximum of 48) into the study at the discretion of the Sponsor.

4.4. Design Justification

As this is the first trial of GSK2982772 in subjects with RA, the primary endpoint is the safety and tolerability of GSK2982772. In addition, this study will include assessments of target engagement and downstream PD effects of GSK2982772, to understand whether GSK2982772 is inhibiting the pathway of interest in this disease.

The 12 week duration of treatment is based on review of previous proof of mechanism and proof of concept studies in RA and is limited by the supporting 13 week toxicology studies. It is expected that an effective therapy should cause group level changes in the mechanistic parameters by the 12 week time point.

The subjects will be randomised in a 2:1 ratio to GSK2982772 60 mg three times daily (TID) and placebo respectively. The primary objective of this study is to assess safety and tolerability, and assessment of this is most valuable in a placebo controlled study.

The placebo group was also deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication and dose is stable throughout the study.

4.5. Dose Justification

The initial selection of the 60 mg BID dose being tested in this study is based on the safety, PK, and PD data from the First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was initially selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2h). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose was predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects will have >90% target engagement in blood at C_{min} using a novel in-house ex-vivo PD/target engagement assay based solely on the TNF pathway which is believed to be a key component of the RIP1 pathway.

However, based on final PK/PD modelling from the full repeat dose part of the Study 200975 (up to 120 mg BID), a 60 mg BID dose is now predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >85% target engagement at C_{min}. This is lower than our target of achieving >90% target engagement in at least 90% of subjects at C_{min}. Therefore, a 60 mg TID cohort is now being proposed.

The C_{min} values at 60 mg TID are predicted to be approximately 3.5 fold higher than for 60 mg BID. Using the final PK/PD, a 60 mg TID dose is predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >96% target engagement at C_{min}. No data are currently available about the distribution of GSK2892772 into the synovium. Based on data in non-steroidal anti-inflammatory drugs (NSAIDs), the synovial fluid concentrations fluctuate to a much lesser extent than those in plasma [Netter, 1989]. Peak drug concentrations are generally lower in synovial fluid but are similar to plasma at later time points. Assuming the same is true for GSK2982772, a 60 mg TID dose should provide similar RIP1 target engagement at the site of action as predicted in blood.

In addition, because of the short half-life, a modified release formulation is now being developed with the aim to provide a once daily dosing regimen. By increasing the frequency of dosing to three times daily (TID) with the current immediate release formulation, this will more closely match the PK, safety and efficacy profile of a preferred once daily modified release formulation.

The safety of increasing the dose frequency to 60 mg TID is justified based on nonclinical safety findings to date with GSK2982772. It is anticipated that a human dose of 60 mg TID (180 mg/day) will produce $AUC_{(0-24)}$ and C_{max} values of approximately 9.9 ug.h/mL and 0.8 ug/mL, respectively, which are approximately $1/5^{th}$ and $1/15^{th}$ of the

gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

As of 03 Apr 2017, a total of approximately 93 subjects across 4 clinical studies have been randomised to receive GSK2982772. In Study 200975, GSK2982772 administered up to 120 mg BID for 14 days and was well tolerated and no safety concerns were identified. A total of 9 subjects had received 120 mg BID in that study. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. In the ongoing Phase 2a studies in Psoriasis [(PsO); Study 203167] and Rheumatoid Arthritis [(RA); Study 203168], a total of 26 subjects have been randomised to GSK2982772 60 mg BID. GSK2982772 was well tolerated and no drug-related SAEs have been reported. In Study 203167, there was a death of a 19 year old male subject due to an accidental overdose with 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the IB [GlaxoSmithKline Document Number 2014N204126_02]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2982772		
Central Nervous System (CNS) effects	**Non-clinical data**: In the 4-week GLP toxicology study, CNS findings were observed in 4/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance, and decreased activity. The clinical relevance of these findings in humans is not known. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical data**: A First Time in Human (FTiH) study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date. See Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_02]. No drug-associated CNS adverse events were identified and no Serious Adverse Effects (SAEs) were reported.	**Subject Selction**: • Subjects with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening. **Subject Monitoring**: • Subjects will be monitored for standard CNS-related adverse events.
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids.	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, HIV, Hepatitis B and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: In the FTiH study, no SAEs were reported. One subject experienced an Adverse Effect (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded Investigator determined this to be potentially drug-related.	C, and excluded from the study if positive. **Subject Monitoring**: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 5.4.1).
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in subjects with RA.
Respiratory	**Non-clinical data**: In the single dose Safety Cardiovascular (CV) and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (minute volume) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02].	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related adverse events. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: In the FTiH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related adverse events were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based upon pre-clinical studies. **Clinical data**: In the FTiH study, there have been some reports of lethargy, abnormal dreams, and depressed mood. No events of suicidal ideation or behaviour or changes in behaviour were reported.	**Subject Selection**: • Subjects with a current history of suicidal ideation and behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel using the (Columbia Suicide Severity Rating Scale) C-SSRS in all subjects. See Section 7.3.7.
Reproductive toxicity	**Non-clinical data:** In an early rat embryofetal development study, there was no maternal or developmental toxicity at doses ≤200 mg/kg/day. In a rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection**: • Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 30days (females) and 90 days (males) after the last administration of study drug (Appendix 6). • Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and OAT3 substrates were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. MTX is an OAT3 substrate in which GSK2982772 could potentially impair the clearance of MTX. There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772. GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772. See Section 4.3.6 of the GSK2982772 IB [GlaxoSmithKline Document 2014N204126_02].	**Subject Selections**: • Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. See Section 6.11.2 for a comprehensive list of medications. **Subject Monitoring:** • Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. • Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications. • PK sample collection to evaluate the potential interaction of GSK2982772 and MTX will be performed throughout the study. • Subjects should be monitored for potential effects of interaction between GSK2982772 and MTX. • Clinical laboratory results (e.g., liver function tests) are routinely being monitored throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Synovial Joint Biopsy	Potential risks of the procedure include discomfort, infection or bleeding. **Note**: Synovial biopsies are optional and not required on all subjects.	**Subject Selection:** • Subjects with known allergy to lidocaine or other local anaesthetics will not be included in the biopsy portion of the study. • Subjects with a platelet count $\leq 100 \times 10^9$/L will be excluded from participation. **Subject Management**: • The biopsies will be performed under ultrasound or arthroscopic guidance. Subjects will be given instructions for aftercare and contact information should there be any adverse reactions after the procedure. • Biopsy site healing will be monitored during the study as part of AE safety review.
Gadolinium (Gd) containing MRI contrast agents	**Non-clinical data**: Animal studies have shown reproductive toxicity of gadolinium (Gd)-containing MRI contrast agents at repeated high doses. **Clinical data**: Use of MRI contrast agents in subjects with severely impaired rental function (GFR<30mL/minute) has been associated with Nephrogenic Systemic Fibrosis (NSF). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed against the risks. Gadolinium (Gd) contrast agents can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory, or	**Subject Selection:** • Pregnant or lactating females will be excluded from taking part in the study. • Subjects with impaired renal function (GFR<60mL/minute) are excluded by the eligibility criteria. • Subjects with history of sensitivity to Gd-containing contrast agents will be excluded from the study. The MRI procedure will be conducted under the supervision of trained and qualified clinical staff that is trained to appropriately manage an allergic reaction. • Sites will be responsible for following any additional safety information for the specific Gd contrast agent used at their site and not enroll subjects if contraindicated.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	cutaneous manifestations, and ranging to severe reactions including shock. In general, subjects with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions. The risk of hypersensitivity reactions may be higher in cases of: • Previous reaction to contrast media • History of bronchial asthma • History of allergic disorders Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely observed.	**Subject Monitoring and Management**: • MRI contrast at a dose less than or equal to 0.1 mmol/kg per imagining session at baseline and Days 43 and 85 will be used in the MRI protocol. • Effective contraception is required during the study, and pregnancy testing will be performed regularly throughout the study and prior to dosing in females of child bearing potential.
Other		
Exposure to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner.	**Subject Selection:** • All participants will be screened according to local hospital criteria and study inclusion/exclusion before entering the MRI scanner to ensure they are able to have the MRI conducted. Subjects with non-magnetic resonance compatible metal implants or implantable electronic devices (e.g., pacemaker, defibrillator) will not be included in this study.

4.6.2. Benefit Assessment

There are additional treatment options available for subjects who have an inadequate response to current therapies for RA. It is possible that treatment with GSK2982772 may be effective in the treatment of RA, as the FTiH study demonstrated that the drug engaged with the target and produced *ex vivo* PD effects in suppression of RIP1-dependent cytokines MIP1α and MIP1β [GlaxoSmithKline Document Number 2014N204126_02]. There will be limited direct benefit to the subject through their contribution to the process of developing new therapies in an area of unmet need.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded to patients with RA by contributing to the understanding of the disease and the development of new therapies for patients with these conditions in the future.

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 (IP) or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number 2014N204126_02].

In addition, Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including vaccinations for influenza and pneumococcus, in subjects with RA.

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

5.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects that do not have any medical conditions, other than moderate to severe RA that in the opinion of the Investigator put the subject at unacceptable risk or interfere with study assessments or integrity of the data. These medical conditions should be

stable at the time of screening and are expected to remain stable for the duration of the study.

3. Subject has had a confirmed diagnosis of rheumatoid arthritis according to the revised 2010 American College of Rheumatology/European League Against Rheumatism ACR-EULAR classification criteria.
4. Disease duration of ≥12 weeks (time from onset of patient-reported symptoms of either pain or stiffness or swelling in hands, feet or wrists) at screening.
5. Swollen joint count of ≥4 (28-joint count) and tender joint count ≥4 (28-joint count) at screening.
6. Subject has a DAS28 CRP disease activity score of ≥3.2 and CRP ≥5.0 mg/L (≥4.76 nmol/L) at screening.
7. Subject must have received at least 12 weeks of non-biologic DMARD monotherapy or methotrexate (MTX)/DMARD combination therapy prior to screening AND must be on stable dose throughout the study.
8. Subject is naive to any biological therapies for RA

   OR

   Subject may have had previous exposure to a single anti-TNF biologic agent which was discontinued for reasons other than primary non-response more than 8 weeks (or 5 half lives whichever is longer) from first dose. **Note: Exposure to a single anti-TNF is not required in addition to Inclusion #7 above.**
9. For subjects who have consented to synovial joint biopsy:
   a. Subject has an involved knee, wrist, or ankle suitable for biopsy, as assessed by a rheumatologist at screening.

WEIGHT
10. A body mass index (BMI) within range of 18.5 - 35 kg/m^2 (inclusive) at screening.

SEX
11. Male and female subjects **Males:** Male subjects with female partners of child bearing potential must comply with the following contraception requirements in Appendix 6. **Females**: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation

- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

- Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods (see Appendix 6) if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 6) from 30 days prior to the first dose of study medication and until at least 30 days after the last dose of study medication and completion of the follow-up visit.

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

INFORMED CONSENT
12. 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. Subject with a positive anti-double stranded deoxyribonucleic acid (DNA [anti-dsDNA]) and confirmed diagnosis of systemic lupus erythematosus (SLE). 2. Subject with current history of Suicidal Ideation Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide. 3. An active infection, or a history of infections as follows: • Hospitalisation for treatment of infection within 60 days before first dose (Day 1). • Currently on any suppressive therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and

atypical mycobacteria).

- Use of parenteral (IV or intramuscular) antibiotics (antibacterials, antivirals, antifungals, or antiparasitic agents) for an infection within 60 days before first dose.
- A history of opportunistic infections within 1 year of screening (e.g. pneumocystis jirovecii, CMV pneumonitis, aspergillosis). This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or recurrent nature.
- Recurrent or chronic infection or other active infection that, in the opinion of the Investigator might cause this study to be detrimental to the patient.
- History of TB, irrespective of treatment status.
- A positive diagnostic TB test at screening defined as a positive QuantiFERON-TB Gold test or T-spot test. In cases where the QuantiFERON or T-spot test is indeterminate, the subject may have the test repeated once, but they will not be eligible for the study unless the second test is negative. In cases where the QuantiFERON or T-spot test is positive, but a locally-read follow up chest x-ray, shows no evidence of current or previous pulmonary tuberculosis, the subject may be eligible for the study at the discretion of the Investigator and GSK Medical Monitor.

4. QTc >450msec or QTc >480msec for subjects with bundle branch block at screening.

   The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual over read.

   The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined and documented prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
5. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
6. Current active or chronic history of liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. Current or history of renal disease or estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 mL/min/1.73m^2 at screening.
8. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
9. A major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
10. Any planned surgical procedures including surgical joint procedures (e.g., intra-articular, tendon sheath, or bursal corticosteroid injections) during the study.
11. A history of malignant neoplasm within the last 5 years, except for adequately treated

non-metastatic cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix that has been fully treated and shows no evidence of recurrence.

12. Has undergone surgery including synovectomy or arthroplasty on the joint chosen for biopsy and/or magnetic resonance imaging (MRI).
13. The subject has a history of any other joint disease other than RA at the knee, wrist or ankle joint chosen for biopsy and/or MRI (e.g., gout, pseudogout, osteoarthritis).
14. Has undergone intra-articular corticosteroid injection, arthrocentesis or synovial biopsy on any joint within 6 weeks of screening.
15. A known allergy to lidocaine or other local anaesthetics (**Note**: only applies to subjects who consent for synovial biopsy procedures).
16. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but are not limited to:
    - Intracranial aneurysm clips (except Sugita) or other metallic objects,
    - History of intra-orbital metal fragments that have not been removed by a medical professional.
    - Pacemakers or other implanted cardiac rhythm management devices and non-MR compatible heart valves,
    - Inner ear implants,
    - History of claustrophobia which may impact participation.

CONCOMITANT MEDICATIONS
17. The subject has received treatment with the therapies listed in Section 6.11.2, or changes to those treatments, within the prescribed timeframe. If in doubt, or the therapy is not listed please consult with the medical monitor. • 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
18. History of alcohol or drug abuse that would interfere with the ability to comply with the study.

CONTRAINDICATIONS
19. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation. 20. Received a live or attenuated vaccine within 30 days of randomization OR plan to receive a vaccination during the study until 5 half-lives (or 2 days) plus 30 days after receiving GSK2982772. 21. Contraindication to gadolinium contrast agent in accordance with local guidelines. 22. The subject has participated in a clinical trial and has received an investigational

product within 30 days or 5 half-lives, whichever is longer before the first dose of study medication, or plans to take part in another clinical trial at the same time as participating in this clinical trial.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
23. Haemoglobin <9 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L); platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at screening. 24. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. As potential for and magnitude of immunosuppression with this compound is unknown, subjects with presence of hepatitis B core antibody (HBcAb) should be excluded. 25. A positive serology for human immunodeficiency virus (HIV) 1 or 2 at screening. 26. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months. 27. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dose.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5).

Subjects who do not qualify to participate in the study due to a screening laboratory value or ECG abnormality can repeat the test once within the original screening window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

Subjects can be re-screened only on approval of the GSK Medical Monitor and only once. Re-screening is allowed when a subject failed inclusion/exclusion criteria or some other screening condition initially, but the Investigator believes there is a reasonable probability that the subject would be eligible if re-screened.

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 Case Report Form (CRF).

- The Sponsor's request, for reasons such as significant protocol deviations or subject safety concern (and after discussion with the Investigator).
- If a subject is withdrawn from study treatment, this subject is also considered to be withdrawn from the study.
- Study is terminated by the Sponsor.

If a subject is withdrawn, the Sponsor may decide to replace that subject and this will be done through the Interactive Response Technology System (IRTS).

If a subject chooses to withdraw from the study after dosing then the Investigator must make every effort to complete the follow-up assessments detailed in the Time and Events Table (Section 7.1).

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

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

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 medications for the treatment of RA as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or Haematologic stopping criteria (Section 5.4.5) are met.
- The subject experiences any signs of suicidal ideation or behaviour (Section 7.3.7).

5.4.2. Group Safety Stopping Criteria

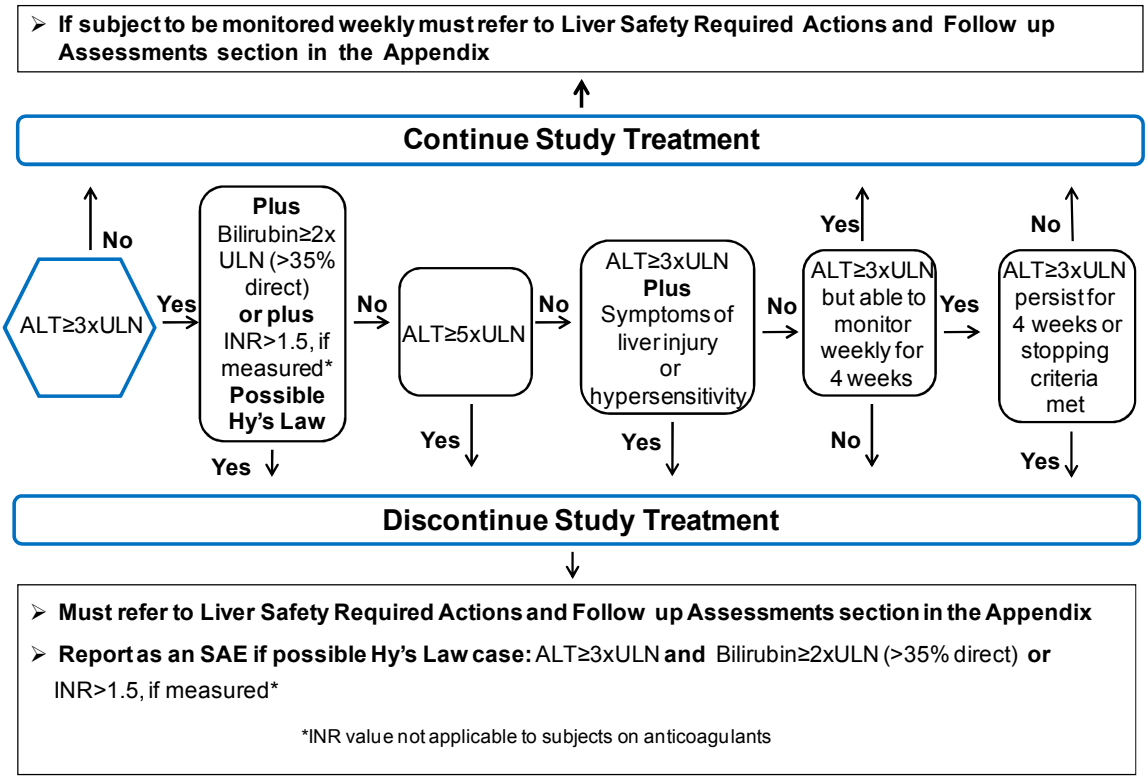
In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subjects will be regularly reviewed by the Sponsor Safety Review Team (SRT) in order to ensure appropriate subject safety. Any changes to the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

5.4.3. 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

Figure 3 Phase II Liver Chemistry Stopping Criteria – Liver Stopping Events Algorithm



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

5.4.3.1. 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.

5.4.4. QTc Stopping Criteria

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

- 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 decision to withdraw a subject will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.4.5. Haematologic Stopping Criteria

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

- Haemoglobin - an absolute decrease of ≥2 g/dL from baseline (pre-dose Day 1)
- Platelets $<50 \times 10^9$/L

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 study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions (with amendment 03):	Take TWO tablets three times a day as directed by your physician	Take TWO tablets three times a day as directed by your physician
Dosing instructions (prior to amendment 03):	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Physical description:	White to almost white, round, film coated tablet	White to almost white, round, film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

6.2. Treatment Assignment

At Screening a unique Subject Number will be assigned to any subject who has signed a consent form. The unique Subject Number will be used to identify individual subjects during the course of the study. Any subject that is re-screened outside of the allowed screening window at the approval of the GSK Medical Monitor, must be assigned a new unique Subject Number.

Subjects who meet screening eligibility criteria will be randomised to a treatment group through an Interactive Response Technology System (IRTS). The IRTS will confirm the subject's CRF number (Subject Number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other subject in the study.

Therefore, the randomisation is centrally controlled by the IRTS.

Subjects will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio.

6.3. Planned Dose Adjustments

No dose adjustments are allowed.

6.4. Blinding

This will be a double blind (sponsor unblinded) study and the following will apply:

- Sponsor unblinded refers only to the Data Review Committee, consisting of the GSK Project Physician Lead (PPL), study statistician, study pharmacokineticist, Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head, Early Development Lead (EDL) and Safety Review Team (SRT) Leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.
- The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator. Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject to his/her study staff or GSK, 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.
- A subject will be withdrawn if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (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.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing.

When subjects self-administer study treatment(s) at home, compliance with GSK2982772 and placebo will be assessed and documented through the review of the subject's diary card and querying the subject during the site visits. A record of the number of GSK2982772 or placebo tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

Subjects will be given instructions on compliance and treatment with MTX (if applicable). The date, time and total weekly dose will be recorded in the study diary cards and the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 >180 mg daily will be considered an overdose. GSK does not recommend specific treatment for an overdose. The Investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

In the event of an overdose, the Investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) for at least 48 hours following the last dose of GSK2982772.
3. Obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document all details of the overdose 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

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

Subjects will not receive any additional treatment from GSK after completion of the study because the 12 week duration of treatment is limited by the supporting 13 week toxicology studies.

6.10. Lifestyle and/or Dietary Restrictions

- Subjects must adhere to the contraceptive requirements listed in Appendix 6.

6.10.1. Activity

- Subjects will abstain from strenuous exercise more than their normal routine for 48 hours prior to each blood collection for clinical laboratory tests.
- Subjects who have consented to synovial biopsies will abstain from strenuous exercise for 24 hours after synovial biopsy procedures.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Selected medications for the treatment of RA may be taken, with specific requirements listed in Table 1, and as long as they are not prohibited (Section 6.11.2). All concomitant medications taken during the study will be recorded in the source document and CRF. The minimum requirement is that drug name and dates of administration are recorded.

Table 1 Specific Requirements for Permitted Medications During the Study

Drug	Requirement
Methotrexate	Stable dose regimen (up to 25 mg/week) for at least 12 weeks prior to screening and remain on this dose throughout the study (unless dose must be reduced because of a safety concern). MTX should ideally be taken on the same day of week and at approximately the same time of day throughout the study.
Sulfasalazine	Stable dose regimen for at least 12 weeks prior to screening and throughout the study.
Hydoxychloroquine or cholorquinine	Stable dose for at least 12 weeks prior to screening and throughout the study.
Leflunomide	Stable dose for at least 12 weeks prior to screening and throughout the study.
Folate supplements (minimum of 5 mg/week)	If a subject is on folate supplements with MTX treatment, they must be on a stable dose regimen for at least 4 weeks prior to randomization and throughout the study.
Other oral anti-rheumatic therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticords (e.g., prednisolone ≤ 10 mg /day. See Appendix 3 for equivalent doses).	Stable dose regimen for at least 4 weeks prior to screening and throughout the study (unless reduction required due to adverse effects). Omit dose on the morning prior to study visits until after joint assessments.

6.11.2. Prohibited Medications and Non-Drug Therapies

Table 2 lists prohibited medications for defined periods of time before and during the study until after the follow up visit.

Subjects who start prohibited medications or therapies as a treatment for RA or other reasons during the study will be withdrawn from study treatment for safety reasons. If in any doubt, Investigators are advised to discuss medications with the medical monitor.

Table 2 Prohibited Medications

Therapy	Time period
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
Janus Kinase (JAK) Inhibitors	4 weeks prior to screening until after the follow up visit (Day 112).
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112).
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	4 weeks prior to the first dose (Day 1) until after the follow up visit (Day 112).
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time.
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 half lives (whichever is longer) prior to first dose until after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may

Therapy	Time period
	be administered whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM and laboratory manual. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

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

- At study visits, the Patient Reported Outcomes (PROs) should be completed prior to any other study assessments.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak 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.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- 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.

7.1. Time and Events Table

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------X															
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4, 20]						X[4,21]						X[22]	X[16]	

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Study Treatment																
Randomisation		X														
Study medication (three times daily)[8]		X----------												----------X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4,20]						X[4,21]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact. On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.
6. All PRO assessments should be conducted on site before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).
8. Subjects must take study medication three times a day approximately 8 hours apart. Exact time of dosing to be recorded in diary cards. On Day 1, the first study dose will be administered at the site. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71. When clinical laboratory samples are taken on the same day as the MRI, the samples should be taken first prior to the administration of the contrast fluid with MRI. If this is not feasible (i.e. MRI is performed first), it is recommended that a separate IV catheter or straight venipuncture be performed in the *opposite* arm to where the MRI contrast fluid was administered.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours. A trough PK sample will be taken on Day 85 or at Early Withdrawal.
13. Only applicable if subjects are on MTX: PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX should ideally take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits should ideally be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit. A window allowance of $\pm$ 3 days of Early Withdrawal visit is allowed to perform the MRI.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days ($\pm$3 days) after the last dose of study medication.
20. MRI (and if applicable; a biopsy) may be performed during the screening window as an additional visit (if required) up to 7 days before Day 1 to allow sites flexibility in scheduling. The MRI must be completed prior to synovial biopsy (if performed on the same joint). The site should be reasonably confident that the subject has fully qualified for the study (e.g., screening clinical labs, vital signs, physical examination, etc.) before the MRI (and if applicable: a biopsy) is/are performed.

21. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (±3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.
22. For MRI performed on day 85, a visit window of up to 2 days after is allowed in order to perform the MRI.

7.2. Screening and Critical Baseline Assessments

After written informed consent, screening assessments will be performed as outlined in the Time and Events Table (Section 7.1).

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

Medical/medication/mental health and family history, ECG and laboratory tests will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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

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

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The Investigator will be responsible for determining the clinical significance of any results that fall outside of the laboratory normal ranges.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT), which will include 203168 study team members, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

7.3.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 5.

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the time points specified in the Time and Events Table (Section 7.1).

- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.3.1.2. Method of Detecting AEs and SAEs

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

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

7.3.1.3. 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 stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the 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.

7.3.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.3.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 30 up to 90 days (as applicable) after the last dose.
- If a pregnancy is reported within 30 days (90 days in partners) after the last dose then the Investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the head, eyes, ears, nose, throat, skin, thyroid, joint, lymph nodes, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded at the first physical examination.
- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.3.4. Vital Signs

- Vital signs will be measured in a supine or semi-supine position after approximately 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

7.3.5. Electrocardiogram (ECG)

- Triplicate12-lead ECGs will be obtained at screening and single 12-lead ECGs obtained at every time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F or B) intervals. A manual over read is also allowed. Refer to Section 5.4.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period.
- ECG to be measured in a semi-supine position after approximately 5 minutes rest.

7.3.6. Clinical Safety Laboratory Assessments

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

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

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

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

- Haematology, platelets and coagulation sample if they are required to be taken closer to the biopsies (as per local practices) than specified in Section 5.4.5.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology [1,2]	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [3]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose[4]	Calcium	Alkaline phosphatise	Albumin
	CRP	Triglycerides[4]	Total Cholesterol[4]	Fasting HDL cholesterol[4]
	Fasting LDL cholesterol[4]			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening and RoutineTests	• HIV 1 & 2 • Hepatitis B (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis C (Hep C antibody) • QuantiFeron Gold Test • T-spot (if QuantiFeron is indeterminant) • FSH and estradiol (as needed in women of non-child bearing potential only) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [5] • Serum hCG (as needed for women of child bearing potential) to be done at screening and if urine test positive at other time points in the study. • Anti-dsDNA • Rheumatoid Factor • Anti-CCP • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula.			

Footnotes:

1. The subject's CBC results from the previous scheduled visit should be checked prior to the synovial biopsy procedures according to local practices and may be repeated at the discretion of the investigator.

2. Details of Haematologic Stopping Criteria are given in Section 5.4.5.
3. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.3 and Appendix 2.
4. No fasting required. Any abnormal result for glucose or lipids (non-fasted) may be repeated at the discretion of the Investigator.
5. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

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

7.3.7. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with RA. Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. Study medication must be immediately discontinued in all subjects who experience signs of suicidal ideation or behaviour.

Families and caregivers of subjects being treated with GSK2982772 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study Investigator.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening CSSRS' will be completed. Assessments will be done at Days 43 (Week 6) and 85 (Week 12), the 'Since Last Visit CSSRS' will be completed. GSK Version 4.1 of both rating scales will be used.

Subjects who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their GP or appropriate psychiatric care and be discontinued from study medication. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 7.3.1 AE and SAE). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

7.4. Efficacy

7.4.1. Patient Reported Outcomes

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

7.4.1.1. Rheumatoid Arthritis Symptoms and Impact Diary

Symptoms associated with RA will be assessed using a novel RA Symptom and Impact Diary as per Section 7.1, Time and Events Table. The study staff should not clarify any of the questions for the subject.

7.4.1.2. Patient Assessment of Joint Pain

The severity of the subject's joint pain will be assessed by completion of a numeric rating scale (NRS). The subject will be asked to select a whole number (0-10 integers) that best reflects the intensity of their pain. The scale is represented by a horizontal bart with "no pain" at the lower anchor and "most severe pain" at the upper anchor. This questionnaire should take approximately 1 minute to complete.

The patient assessment of joint pain will be used to calculate ACR responders.

7.4.1.3. Patient's Global Assessment of Disease (PtGA)

Subjects will complete a global assessment of disease activity using the patient global assessment item, a visual analogue scale (VAS) with anchors "0" (very well) to "10" (very poor).

The patient's global assessment of disease will be used to calculate DAS clinical scores and ACR responders.

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

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.

This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas [Fries, 1980]:

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

Responses are scored from 0 (no difficulty) to 3 (inability to perform a task in that area).

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

7.4.1.5. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale

Subjects will complete a 13-point fatigue questionnaire using the FACIT-Fatigue assessment, a Likert scale from 0 to 4, to "0" (very much fatigued) to"4" (not at all fatigued). This questionnaire should take a few minutes to complete and provides the level of fatigue with usual daily activities from the previous week.

7.4.2. Clinical Disease Assessments

Brief details are given below and detailed procedural instructions are given in the SRM. The sponsor will calculate DAS28(CRP) and ACR (20/50/70) responses at each assessment time point as defined below.

7.4.2.1. Disease Activity Score (DAS) Assessments

The DAS28 is a measure of disease activity. It is a composite score derived measurement weighing given to each component.

The components of the DAS28 assessment include:

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

7.4.2.2. American College of Rheumatology Criteria (ACR) Assessments

The ACR Criteria is a standard criteria to measure the effectiveness of treatments from placebo. The ACR's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvement.

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

- Tender/Painful Joint count (28)
- Swollen Joint Count (28)
- Patient Assessment of Joint Pain
- PtGA
- PGA
- CRP
- HAQ-DI

7.4.2.3. Joint Assessments

Tender Joint Count Assessments
A total of 28 joints will be scored for presence or absence of tenderness.

Swollen Joint Count Assessments

A total of 28 joints will be scored for presence or absence of swelling.

Joint assessments will be used to calculate DAS28 clinical scores and ACR responders.

7.4.2.4. Measurement of Serum CRP

Blood samples will be collected in order to measure serum CRP concentrations. The CRP is a component of the DAS28, ACR, and Vectra DA clinical scores.

7.4.2.5. Physician's Global Assessment of Disease Activity (PGA)

The Investigator or physician designee only will complete a global assessment of disease activity using the physician global assessment item, a VAS with anchor's "0" (none) to "10" (extremely active).

Note:

- The Investigator or physician designee should complete the PGA independently of the subject.
- Ideally, the same Investigator or physician designee should perform all global assessments for each subject during the duration of the study.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for PK analysis of GSK2982772 will be collected at the time points indicated in Section 7.1 Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

For subjects who are on stable doses of methotrexate (MTX), blood samples for PK analysis of MTX will be collected at the time points indicated in Section 7.1 Time and Events Table. The actual date and time of each blood sample collection will be recorded.

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

7.5.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of GSK2982772

and MTX will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma sample has been analysed for GSK2982772 any remaining plasma sample may be analysed for other compound-related material and the results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.5.3. Synovial Biopsy Tissue for Pharmacokinetic Assay

See Section 7.6.2.2 for details on synovial tissue biopsy and procedure. If available, synovial tissue samples may be analysed for concentrations of GSK2982772 and possible drug-related material, as well as specific tissue distribution if feasible as sample availability allows.

7.5.4. Sample Analysis

Synovial biopsy sample analysis will be performed under the control of PTS IVIVT, GlaxoSmithKline. Information on processing the biopsies for the synovial pharmacokinetic assay will be provided in the laboratory manual. The results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.6. Biomarker(s)/Pharmacodynamic Markers

Pharmacodynamic biomarkers will be collected at the time points in Section 7.1 Time and Events Table and may include, but are not limited to, the following:

- Blood samples for mRNA expression e.g., IL6, MMP-1, MMP3, MMP-13, TIMP-1, MCP-1 and MIF.
- Blood samples for biomarkers which may be indicative of RA disease activity e.g., MRP8/14 and markers encompassed by Vectra DA.

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

7.6.1. Magnetic Resonance Imaging (MRI) of Joint

The most affected hand will be documented at baseline and used for all imaging visits. If subjects report both hands are equally involved, then the subject's dominant hand will be used.

DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability, only a standard MRI will be performed.

Each subject's most affected wrist (corresponding to the affected hand which is determined and documented at baseline) will be imaged by MRI at pre-dose on Days 1, 43 and 85 (see Section 7.1). If a scanning failure occurs at any visit, if feasible a rescan

is allowed within 7 days after the failed scan after consultation and agreement with the GSK Medical Monitor. There will be a minimum of 24 hours between scans where gadolinium (Gd) contrast is used. The MRI will be used in order to non-invasively quantify the degree of inflammation and structural changes within the target joint.

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

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

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

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

7.6.2. Synovial Biopsy

7.6.2.1. Selection of Joint for Synovial Biopsy

Synovial biopsies are optional for subjects enrolled in this study. There is no minimum number of subjects with joint biopsies required, but biopsies should be performed in as many subjects as possible. Synovial biopsy of a subject's swollen and tender wrist, knee or ankle joint will be performed at baseline (pre-dose Day 1). The final choice of joint is left to the discretion of the Investigator, although ideally it will be the most inflamed joint. The same joint should be biopsied at Day 43 (Week 6). If in the event that a repeat biopsy of the same joint as baseline is not possible, the joint may change if essential, after discussion with the GSK Medical Monitor. Any change must be documented in the CRF.

If a subject chooses to withdraw from the study after dosing and prior to Day 43, the Investigator must make every effort to perform a synovial biopsy if the subject has received at least 14 days of treatment with GSK2982772 or placebo.

7.6.2.2. Synovial Biopsy Procedure

Ultrasound imaging or arthroscopy will be used to guide the collection of approximately (as feasible for any given subject) of 6 synovial biopsies for immunohistochemistry (IHC), 6 synovial biopsies for pharmacokinetics, 6 synovial biopsies for target engagement, and 6 synovial biopsies for RNA extraction up to a combined maximum of 30 biopsies from the chosen joint under local anaesthesia (see SRM).

Biopsy tissue taken from synovial tissue will be divided accordingly for IHC, PK, target and pathway engagement, and gene expression. Histological assessment by IHC will be evaluated for general appearance and total inflammatory infiltrate. Specific cell numbers will also be analysed (which may include but are not limited to CD3+T-cells, CD55+ fibroblast-like synoviocytes, CD68+macrophages). mRNA may be isolated from synovial biopsys tissue, as feasibility dictates, to determine the effect of placebo and GSK2982772 on markers of inflammation and tissue healing (e.g., may include and not be limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1 and other chemokines and cytokines). Biopsy tissue collected for RNA transcriptional analysis may be utilised to determine the effect of GSK2982772 on cytokine and receptor expression, in addition to other markers of inflammation and tissue healing, as feasibility allows. For example, this may include but is not limited to, measurement of acute phase proteins, other chemokines and cytokines. Examples of technologies that may be used for these analysis include, but are not limited to, quantitative PCR, microarray, RNA sequencing or mass cytometry (CyTOF).

7.6.3. Novel Pharmacodynamic Biomarkers

7.6.3.1. RIP1 Target Engagement in Blood

Blood samples for RIP1 target engagement will be collected at the time points indicated in Section 7.1 to measure levels of free and drug-bound RIP1 protein.

7.6.3.2. RIP1 Target Engagement in Synovial Tissue

Synovial tissue biopsy samples will be collected at the time points indicted in Section 7.1 to measure levels of free and drug-bound RIP1 protein if sample quantity and data allow.

7.6.3.3. Pathway Biomarkers in Synovial Tissue

Synovial tissue biopsy samples will be collected at the time points indicated in Section 7.1 to measure total or phosphorylated RIP1, RIP3, MLKL and cleaved or total caspase 3 and caspase 8 if sample quantity and data allow.

7.6.4. Exploratory Novel Biomarkers

With the subject's consent, tissue and blood sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence disease/condition for study treatment, and/or medically related conditions, as well as the biological and clinical responses to GSK2982772. 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 GSK2982772 may be identified by application of:

- Gene expression analysis may be conducted on the blood and/or synovial biopsies using microarray, RNA sequencing and/or alternative equivalent technologies, which facilitates the simultaneous measurement (and confirmation) of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each synovial tissue sample.
- Soluble inflammatory mediators in the blood may be assayed for cytokine and inflammatory mediators including, but not limited to, pro-inflammatory and anti-inflammatory cytokines, chemokines, and acute phase proteins.

These analyses may be reported under separate protocol following the completion of the study. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

7.7. Genetics

In consenting subjects, a blood sample for pharmacogenetics (PGx) research will be drawn on Day 1 (or any time point post randomisation and prior to study completion) to better characterize genetic variability that may affect efficacy or safety endpoints. Information regarding pharmaogenetic (PGx) research is included in Appendix 4.

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 and date of birth will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of the study is to investigate the safety and tolerability of GSK2982772 following 12 weeks of treatment. No formal statistical hypotheses will be conducted to assess this objective.

If appropriate, comparisons between the GSK2982772 and the placebo arm will be made to investigate the secondary pharmacodynamic, mechanistic and efficacy objectives.

Trends over time will be investigated for both treatment arms along with associations between each of the pharmacodynamic, mechanistic and efficacy parameters.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

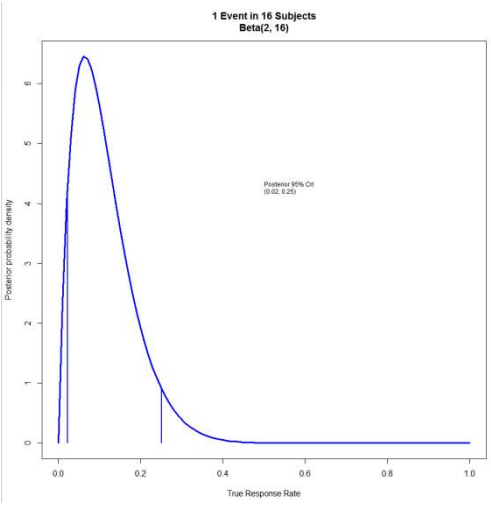
The study is not powered to detect pre-defined differences. A sufficient number of subjects will be screened so that approximately 24 subjects with moderate to severe RA are randomised into the study on a TID regimen. Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Table 4 summarises the total planned sample sizes for BID and TID regimens. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to an overall total maximum of 48) into the study at the discretion of the Sponsor.

Table 4 Summary of Total Sample Size by Dosing Regimen

Number Randomised to GSK2982772 60 mg BID or Placebo BID	Number Randomised to GSK2982772 60 mg TID or Placebo TID	Revised Max Total Sample Size	Total + Additional/ Replacement Subjects
7 - 12	24	36	42
12 - 18	24	42	48

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772 60 mg TID and up to 12 subjects randomised to GSK29827772 60 mg BID. Using a Bayesian approach to determine the confidence interval (CI) around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 16 then the posterior distribution would be Beta (2, 16), as outlined below in Figure 4.

Figure 4 One Event in 16 Subjects: Beta (2,16) Distribution



Thus, we can be 95% certain that the true probability of the safety event lies between 2% and 25%.

For supportive information, the properties of the key secondary endpoint DAS28 have been considered.

Based on the estimate of variability (SD=1 from historical data) it is estimated that the lower and upper bounds of the 95% CI for the change from baseline in DAS28-CRP score will be within approximately 0.693 and 0.490 of the point estimate of GSK2982772 60 mg TID (n=16) and placebo (n=8).

9.2.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is higher or lower than 16 in the GSK2982772 group, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in Table 5.

Table 5 Sample Size Sensitivity

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
20	0	16.1%
20	1	23.8%
20	2	30.4%
18	0	17.6%
18	1	26.0%
18	2	33.1%
16	0	19.5%

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
16	1	28.7%
16	2	36.4%
14	0	21.8%
14	1	31.9%
14	2	40.5%
12	0	24.7%
12	1	36.0%
12	2	45.4%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be conducted.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All Subjects Population: The 'All Subjects Population' is defined as subjects who were screened for the study. This population is used for the summary of selected accountability data.

Safety Population: The 'Safety Population' is defined as subjects who receive at least one dose of study medication. This population is used for the summary of all data including demography, safety, efficacy and exploratory data but excluding PK data.

Pharmacokinetic Population: The 'PK Population' is defined as subjects in the 'Safety' population who received an active dose and for whom a GSK2982772 pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only. Any PK-PD analysis will be conducted on the Safety population such that subjects receiving placebo can be included.

If 12 or more subjects are randomised to a BID regimen (i.e., ≥4 placebo and ≥8 GSK2982772 60 mg BID) then treatment received will take into account dosing frequency for GSK2982772, otherwise treatment will be irrespective of dosing frequency.

9.3.2. Interim Analysis

A formal interim analysis will be conducted during the study. Additionally two review teams will monitor data on an ongoing basis for routine pharmacovigilance and decision making regarding the subsequent clinical development of GSK2982772 for RA.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT) which will include members of the GSK2982772 project team, will review blinded safety

data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK Project Physician Lead (PPL), the study statistician, the study pharmacokineticist, the PRR DPU Head, EDL and SRT Leader or designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data. The primary purpose of these informal reviews will be to monitor DAS28-CRP for futility. On review of DAS28-CRP data, the review group may recommend an interim analysis of key clinical and mechanistic data is first conducted prior to any decision to terminate the study for futility. A data review charter will identify the specific GSK individuals involved, outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted during the study. The timing of this analysis will either be on the recommendation of the data review group to assess futility based on 6 weeks of treatment, or when an appropriate number have completed 12 weeks of treatment, whichever is earliest. The purpose of the Interim Analysis would be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

All safety evaluations will be based on the Safety population. Clinical interpretation will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead ECG monitoring.

9.4.2. Secondary Analyses

The relationship between each of the mechanistic endpoints and also with the clinical endpoints will be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g., DAS28-CRP score). This may be conducted through comparing statistical models incorporating different explanatory terms (i.e. mechanistic endpoints) with the 'null' model (no mechanistic endpoints); or if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed.

Each endpoint will be considered individually and at the treatment level, where comparisons between treatment groups would be made on any changes observed, if deemed appropriate. This could include change from baseline in DAS28-CRP, which will be statistically analysed using a MMRM analysis comparing GSK2982772 with placebo

at each time point. Additionally this could include, the proportion of subjects achieving ACR20/50/70 and DAS28-CRP response, which will be statistically analysed using a Generalised Estimating Equation (GEE) model comparing GSK2982772 with placebo at each timepoint. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

9.4.3. Other Analyses

In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain change in DAS28 (i.e., comparator rate), based on the data that we have observed in the study.

GSK2982772 plasma concentrations will be summarised descriptively by day and nominal sampling time.

Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

9.4.3.1. Exploratory Analyses

All exploratory endpoints will be descriptively summarised, graphically presented and listed appropriately. Further details can be found 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

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) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the Investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

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

10.6. Records Retention

- Following closure of the study, the Investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The Investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator is no longer associated with the site.

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

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

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

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

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMD	Age-related macular degeneration
Anti-CCP	Anti-Cyclic Citrullinated Peptide
Anti-dsDNA	Anti-double stranded deoxyribose nucleic acid
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BID	Twice a day
CARLOS	Cartilage Loss Scoring System
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-Reactive Protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CYP	Cytochrome P
DAS	Disease Activity Score
DAS28	Disease activity score for 28 different joints
DAS28(CRP)	Disease activity score for 28 different joints with CRP value
DCE	Dynamic contrast enhanced
DNA	Deoxyribose Nucleic Acid
DMARD	Disease-Modifying Antirheumatic Drugs
DPU	Discovery Performance Unit
DRC	Data Review Committee
ECG	Electrocardiogram
EDL	Early Development Lead
EMA	European Medicines Agency
ETCO2	End-tidal Carbon Dioxide
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTiH	First Time in Human
GCP	Good Clinical Practice

Gd	Gadolinium
GEE	Generalised Estimating Equations
GFR	Glomerular Filtrate Rate
GSK	GlaxoSmithKline
HAQ-DI	Disability Index of the Healthy Assessment Questionnaire
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
IRE	Initial rate of enhancement
IRTS	Interactive Response Technology System
Kg	Kilogram
L	Litre
LDL	Low Density Lipoprotein
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxy-methamphetamine
ME	Maximal signal intensity enhancement
MedDRA	Medical Dictionary for Regulatory Activity
mg	Milligram
mL	Millilitre
MLKL	Mixed lineage kinase domain-like protein
mm	Millimeter
mmol	Millimole
MMP	Matrix metallopproteinase
MMRM	Mixed-effect Model Repeat Measurements
MRI	Magnetic Resonance Imaging
msec	millisecond
MRP	Myeloid-related Protein
MSDS	Material Safety Data Sheet
MTX	Methotrexate
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NOAEL	No Adverse Effect Level
NONMEM	Non Linear Mixed Effect Model
NRS	Numeric Rating Scale

NSAID	Non-steroidal anti-inflammatory drug
NSF	Nephrogenic Systemic Fibrosis
OMERACT	Outcome Measures in Rheumatology
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PGA	Physician's Global Assessment of Disease
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetic
PPD	Tuberculin Purified Protein Derivative
PPL	Project Physician Lead
PRO	Patient Reported Outcome
PRR	Pattern Recognition Receptor
PSRAE	Possible Suicidality Related Adverse Event
PtGA	Patient Global Assessment of Disease
PTS IVIVT	Platform Technology and Science In Vitro/In Vitro Translation
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
R&D	Research and Development
RAP	Reporting and Analysis Plan
RAMRIQ	Rheumatoid arthritis MRI quantitative
RAMRIS	Rheumatoid arthritis MRI scoring system
RBC	Red Blood Cell
RF	Rheumatoid factor
RIP1	Receptor-interacting protein-1
RIP3	Receptor-interacting protein-3
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SIB	Suicidal Ideation Behaviour
SLE	Systemic lupus erythematosus
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SpO2	Peripheral Capillary Oxygen Saturation
SRM	Study Reference Manual
SRT	Safety Review Team
TB	Tuberculosis
TEAR	Target Engagement Assay RIP1
TID	Three times a day
TIMP	Tissue inhibitor of metalloproteinases

TLR	Toll-like receptor
TNF	Tumor necrosis factor
TTS	Technical Terms of Supply
UK	United Kingdom
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
WOCP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
QuantiFERON
Sugita
Vectra DA

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>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, stabilize, or return to within baseline (see MONITORING below)
Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study</td><td>Viral hepatitis serology[4]
Blood sample for pharmacokinetic (PK) analysis, obtained within 2 days after last dose[5]
Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
Fractionate bilirubin, if total bilirubin≥2xULN
Obtain complete blood count with differential to assess eosinophilia
Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
Record use of concomitant medications</td></tr>
</table>

treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<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]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

12.3. Appendix 3: Prednisolone Equivalent Dose Table

Drug Name	**Dose Equivalent to 1 mg Oral Prednisone**
Cortisone acetate	5 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg
Dexamethasone	0.15 mg

12.4. Appendix 4- 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 GSK2982772 or any concomitant medicines;
- Rheumatoid arthritis susceptibility, severity, and progression and related conditions

GSK2982772 is a novel first-in-class asset being introduced to patients with moderate to severe RA for the first time. Currently its mechanism of action is not fully characterised nor understood.

Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance. In addition, continuing research may identify other enzymes, transporters, proteins ore receptors that may be involved in response to GSK2982772. The genes that may code for these proteins may also be studied. Genome-wide scans involving a large number of polymorphic markers (e.g. single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene does not exist and/or the potential genetic effects are not well understood.

Genetic data may be generated while the study is underway or following completion of the study. Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

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

Study Population

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

Study Assessments and Procedures

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

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

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

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK2982772 has been completed and the study data reviewed. In some cases, the samples may not be studied.

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 and Baseline Failures

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

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

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic

studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

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

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

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.5.2. Definition of Serious Adverse Events

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

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

Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Is associated with liver injury and 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

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

12.5.4. 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 PRO questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the PRO 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.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

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

12.5.6. 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 Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The Investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.6.1. 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 sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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

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 90 days after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
   - Contraceptive subdermal implant
   - Intrauterine device or intrauterine system

- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]

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

12.6.2. 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 fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to GSK as described in Appendix 4 While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will discontinue study medication or 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 and up to 90 days after the last dose of study medication. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.

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

12.7. Appendix 7: Protocol Amendment Changes

12.7.1. Amendment 3 (20-APR-2017) from Protocol Amendment 2 (14-JUL-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 03 incorporates change in dosing regimen from 60 mg BID to 60 mg TID, restrictions on JAK inhibitors, defined non-reproductive potential criteria in Exclusion 11, change to clinical laboratory criteria in Exclusion 23, of evaluation of joint space narrowing with MRI, flexibility in scheduling with MRI and synovial biopsy.

GlaxoSmithKline Document Number of Investigator Brochure GSK2982772 has been updated to 2014N204126_02 throughout the document. Other minor protocol clarifications and administrative changes are also provided in this amendment.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Authors

Author (s): PPD

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	**Tel** PPD **Email** PPD ~~Mobile:~~ PPD ~~Email:~~ PPD	**Mobile** PPD PPD PPD ~~Mobile:~~ PP PPD	**N/A** PPD	**GSK Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, UK** ~~UP4440~~ ~~1250 S~~ ~~Collegeville, PA 19426 USA~~
Secondary Medical Monitor		**Mobile:**PPD **Email** PPD ~~Tel:~~ PPD ~~Mobile:~~ PPD ~~Email:~~ PPD	**Mobile**PPD PPD ~~Mobile:~~ PPD PPD	**NA** PPD PPD	**1250 S. Collegeville Rd. Collegeville PA 19426, USA** ~~Cytokine Chemokine DPU, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, UK~~
SAE contact information	Medical Monitor as above				

Synopsis and Section 2.1 Study Rationale

The primary objective of this study has not changed with amendment 03; however the dosing regimen does change to GSK2982772 (60 mg three times daily for 84 days).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg ~~twice~~ **three times daily** for 84 days). In addition to the pharmacokinetics (PK), a number of experimental and clinical endpoints will be employed to obtain information on the pharmacodynamics (PD), and preliminary efficacy in subjects with active RA. Although no formal hypothesis will be tested, these endpoints will enable a broader understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in RA, by making full use of the information obtained from each subject enrolled.

Synopsis and Section 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg ~~twice~~ **three times** daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8 and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 **mg** ~~twice~~ **three times** daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Magnetic Resonance Imaging (MRI) parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, ~~and~~ bone oedema **and joint space narrowing** as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, **the** RAMRIQ (Rheumatoid arthritis MRI quantitative) scoring system, **the modified CARLOS (Cartilage Loss Scoring System)** and additional exploratory endpoints as data permit. • Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:

Objectives	Endpoints
	• Exchange rate (K^{trans}) • Interstitial volume (V_e) • Plasma volume (V_p) • Initial rate of enhancement (IRE) • Maximal signal intensity enhancement (ME) • Joint volume • Enhancing volume
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg ~~twice~~ **three times** daily dosing of GSK2982772 on methotrexate (MTX) concentrations.	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue from subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.

• To investigate pathway and target engagement following 60 mg ~~twice~~ **three times** daily doses of GSK2982772 in blood and synovial biopsy tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit:
	  • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue.
	  • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.

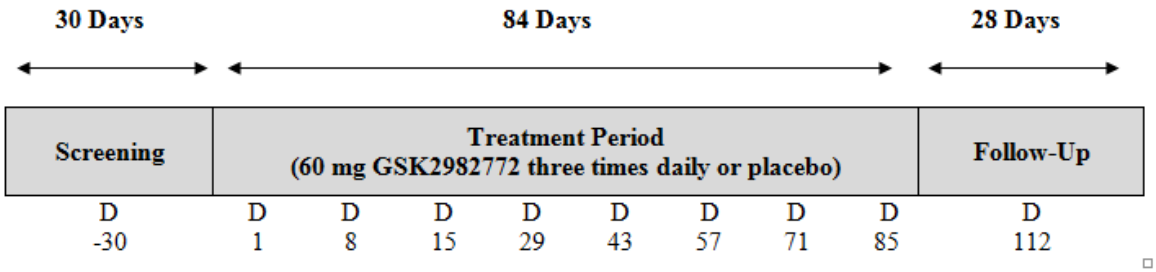
• To investigate the concentration of	• Pre-dose GSK2982772 synovial tissue

Objectives	Endpoints
GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg ~~twice~~ **three times** daily doses of GSK2982772.	biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit.
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on gene expression in the blood subjects with active moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on gene expression in the synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

Synopsis and Section 4.1 Overall Design

Schematic added.

Amendment 03:



Synopsis Treatment Arms and Duration

Subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg ~~twice~~ **three times** daily (~~BID~~ **TID**)

Placebo **three times** daily (~~BID~~ **TID**)

Prior to amendment 03 being effective in each country, subjects have been randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg two times daily (BID)

Placebo two times daily (BID)

Synopsis and Section 4.3 Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately ~~30~~ **24** subjects with moderate to severe RA are randomised into the study **on a TID regimen. Prior to protocol amendment 03 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen**. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to ~~a~~ **an overall total** maximum of ~~36~~ **48**) into the study at the discretion of the Sponsor.

Section 4.2.2 Treatment Period

Subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally ~~twice~~ **three times** daily (approximately ~~12~~ **8** hours apart) for 84 days (12 weeks**). Subjects that were randomised prior to protocol amendment 03 being approved in each country were randomly assigned to either GSK2982772 60 mg or placebo orally two times daily (approximately 12 hours apart) for 84 days (12 weeks).**

During the 84 day (12 week) treatment period, subjects will attend the clinical site for visits on Days 1, 8, 15, 29, 43, 57, 71 and 85. At specific visits, subjects must not take study treatment prior to their scheduled visit (see Section 7.1). On Days 22, 36, 50, 64 and 78, each subject will be contacted by telephone and asked about their general health**, study medication compliance and diary card completion. Subjects will be given a diary card at each of the visits on which they will be instructed** to record their daily study medication and concomitant medication taken and any adverse events.

Section 4.3 Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately ~~30~~ **24** subjects with moderate to severe RA are randomised into the study **on a TID regimen**. **Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen.** Should the **overall** drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to ~~a~~ **an overall total** maximum of ~~36~~ **48**) into the study at the discretion of the Sponsor.

Section 4.4 Design Justification

The subjects will be randomised in a 2:1 ratio to GSK2982772 60 mg ~~twice daily (BID)~~ **three times daily (TID)** and placebo respectively. The primary objective of this study is

to assess safety and tolerability, and assessment of this is most valuable in a placebo controlled study. The placebo group was also deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication and dose is stable throughout the study.

Section 4.5 Dose Justification

The **initial** selection of the 60 mg BID dose ~~to be~~ **being** tested in this study is based on the safety, PK, and PD data from the First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was **initially** selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2h). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose **was**~~is~~ predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects will have >90% target engagement in blood at C_{min} **using a novel in-house ex-vivo PD/target engagement assay based solely on the TNF pathway which is believed to be a key component of the RIP1 pathway**.

However, based on final PK/PD modelling from the full repeat dose part of the Study 200975 (up to 120 mg BID), a 60 mg BID dose is now predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >85% target engagement at C_{min}. This is lower than our target of achieving >90% target engagement in at least 90% of subjects at C_{min}. Therefore, a 60 mg TID cohort is now being proposed.

The C_{min} values at 60 mg TID are predicted to be approximately 3.5 fold higher than for 60 mg BID. Using the final PK/PD, a 60 mg TID dose is predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have > 96% target engagement at C_{min}. No data are currently available about the distribution of GSK2892772 into the synovium. Based on data in non-steroidal anti-inflammatory drugs (NSAIDs), the synovial fluid concentrations fluctuate to a much lesser extent than those in plasma [Netter, 1989]. Peak drug concentrations are generally lower in synovial fluid but are similar to plasma at later time points. Assuming the same is true for GSK2982772, a 60 mg ~~BID~~**TID** dose should provide similar RIP1 target engagement at the site of action as predicted in blood.

In addition, because of the short half-life, a modified release formulation is now being developed with the aim to provide a once daily dosing regimen. By increasing the frequency of dosing to three times daily (TID) with the current immediate release formulation, this will more closely match the PK, safety and efficacy profile of a preferred once daily modified release formulation.

The safety of increasing the dose frequency to 60 mg TID is justified based on nonclinical safety findings to date with GSK2982772. It is anticipated that a human dose of 60 mg TID (180 mg/day) will produce $AUC_{(0\text{-}24)}$ and C_{max} values of approximately 9.9 ug.h/mL and 0.8 ug/mL, respectively, which are approximately

1/5th and 1/15th of the gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

As of 03 Apr 2017, a total of approximately 93 subjects across 4 clinical studies have been randomised to receive GSK2982772. In Study 200975, GSK2982772 administered up to 120 mg BID for 14 days and was well tolerated and no safety concerns were identified. A total of 9 subjects had received 120 mg BID in that study. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. In the ongoing Phase 2a studies in Psoriasis [(PsO); Study 203167] and Rheumatoid Arthritis [(RA); Study 203168], a total of 26 subjects have been randomised to GSK2982772 60 mg BID. GSK2982772 was well tolerated and no drug-related SAEs have been reported. In Study 203167, there was a death of a 19 year old male subject due to an accidental overdose with 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

~~Therefore, it is predicted that a dose of GSK2982772 60 mg BID may be clinically efficacious in subjects with RA.~~

~~It is anticipated that a human dose of 60 mg BID will produce area under the concentration-time curve ($AUC_{[0-24]}$) and maximum observed concentration (C_{max}) values of approximately 9 µg.h/mL and 1 µg/mL, respectively, which are approximately 1/6th and 1/12th of the gender-averaged AUC (48.4 µg.h/mL) and C_{max} (12.3 µg/mL) achieved in the 13-week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day.~~

Section 5.1 Inclusion Criteria

Sex

11. Male & Female subjects

Females:

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

a. Non-reproductive potential ~~as~~ defined **as** ~~in Appendix 6~~:

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

- **Documented Bilateral Oophorectomy**

- **Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods (see Appendix 6) 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.**

Section 5.2 Exclusion Criteria

Diagnostic assessments and other criteria

23. Haemoglobin <~~11~~**9** g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L) ~~or ≥14,000/mm^3 (≥14 x 10^9/L)~~; platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤~~3~~**1.5** x 10^9/L~~; lymphocyte count <1 x 10^9/L~~ at screening.

Section 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 Case Report Form (CRF).
- The Sponsor's request, for reasons such as significant protocol deviations **or subject safety concern** (and after discussion with the Investigator).
- If a subject is withdrawn from study treatment, this subject is also considered to be withdrawn from the study.
- Study is terminated by the Sponsor.

Section 5.4.5 Haematologic Stopping Rules

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~~**2** g/dL from baseline (pre-dose Day 1)
- ~~Neutrophils <1 × 10^9/L~~

- ~~Lymphocytes <0.5 × 10^9/L~~
- Platelets <50 × 10^9/L

Section 6.1 Investigation Product and Other Study Treatment

	Study ~~Treamtent~~ Treatment	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions (with amendment 03):	**Take TWO tablets three times a day as directed by your physician**	**Take TWO tablets three times a day as directed by your physician**
Dosing instructions **(prior to amendment 03):**	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Physical description:	White to almost white, round, film coated tablet	White to almost white, round, film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

Section 6.4 Blinding

Sponsor unblinded refers only to the Data Review Committee (DRC) consisting of the GSK ~~study physician~~ **Project Physician Lead (PPL),** the study statistician, the study pharmacokineticist, Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head, the Early Development Leader (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis.

Section 6.7 Compliance With Study Treatment Administration

Subjects will be given instructions on compliance and treatment with MTX (if applicable). The date, time and total weekly dose will be recorded in **the study diary cards and** the CRF.

Section 6.8 Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 >~~120~~**180** mg daily will be considered an overdose. GSK does not recommend specific treatment for an overdose. The Investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

Section 6.11.1 Permitted Medications and Non-Drug Therapies

Table 1

Drug	Requirement
Methotrexate	Stable dose regimen (up to 25 mg/week) for at least 12 weeks prior to screening and remain on this dose throughout the study (unless dose must be reduced because of a safety concern). MTX should **ideally** be taken on the same day of week and at approximately the same time of day throughout the study.

Section 6.11.2 Prohibited Medications and Non-Drug Therapies

Table 2

Therapy	**Time period**
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
Janus Kinase (JAK) Inhibitors	**4 weeks prior to screening until after the follow up visit (Day 112).**
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112).
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	4 weeks prior to the first dose (Day 1) until after the follow up visit (Day 112).
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time.

Therapy	Time period
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 ~~½~~ **half** lives (whichever is longer) prior to first dose until after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

Section 7.1 Time and Events Table

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------															----------X
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4, 20]						X[4,~~20~~21]						X[22]	X[16]	

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Study Treatment																
Randomisation		X														
Study medication (~~twice~~**three times** daily)[8]		X----------												----------X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4,**20**]						X[4,~~19~~**21**]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).

2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact. On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.
6. All PRO assessments should be conducted **on site** before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).
8. Subjects must take study medication ~~twice~~**three times** a day approximately ~~12~~ 8 hours apart. Exact time of dosing to be recorded in diary cards. On Day 1, the first study dose will be administered at the site. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71. **When clinical laboratory samples are taken on the same day as the MRI, the samples should be taken first prior to the administration of the contrast fluid with MRI. If this is not feasible (i.e. MRI is performed first), it is recommended that a separate IV catheter or straight venipuncture be performed in the *opposite* arm to where the MRI contrast fluid was administered.**
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours. **A**~~and~~ **trough PK sample will be taken** on Day 85 or at Early Withdrawal.
13. **Only applicable if subjects are on MTX:** PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX ~~must~~ should ideally take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits ~~must~~should ideally be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit. **A window allowance of ± 3 days of Early Withdrawal visit is allowed to perform the MRI**.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.
20. **MRI (and if applicable; a biopsy) may be performed during the screening window as an additional visit (if required) up to 7 days before Day 1 to allow sites flexibility in scheduling. The MRI must be completed prior to synovial biopsy (if performed on the same joint). The site should be reasonably confident that the subject has fully qualified for the study (e.g., screening clinical labs, vital signs, physical examination, etc.) before the MRI (and if applicable: a biopsy) is/are performed.**

21. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (±3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.
22. **For MRI performed on day 85, a visit window of up to 2 days after is allowed in order to perform the MRI.**

Section 7.3.5 Electrocardiogram (ECG)

- Triplicate12-lead ECGs will be obtained at screening and single 12-lead ECGs obtained at every time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F or B) intervals. **A manual over read is also allowed.** Refer to Section 5.4.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.

Section 7.3.7 Suicidal Risk Monitoring

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. **Study medication must be immediately discontinued in a**ll subjects who experience signs of suicidal ideation or behaviour ~~must immediately be discontinued from study medication~~.

Section 7.6.1 Magnetic Resonance Imaging (MRI) of Joint

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

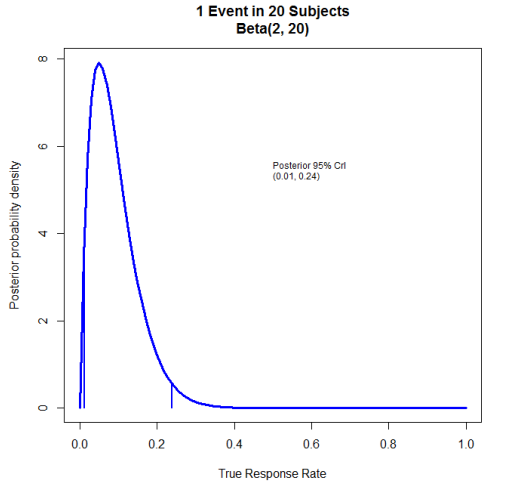
Section 9.2.1 Sample Size Assumptions

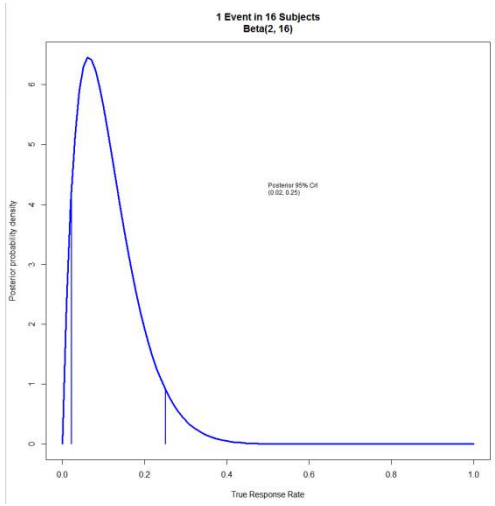
The study is not powered to detect pre-defined differences. A sufficient number of subjects will be screened so that approximately **24**~~30~~ subjects with moderate to severe RA are randomised into the study **on a TID regimen. Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Table 4 summarises the total planned sample sizes for BID and TID regimens.** Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to **an overall** maximum of **48**~~36~~) into the study at the discretion of the Sponsor.

Table 4 Summary of Total Sample Size by Dosing Regimen

Number Randomised to GSK2982772 60 mg BID or Placebo BID	Number Randomised to GSK2982772 60 mg TID or Placebo TID	Revised Max Total Sample Size	Total + Additional/ Replacement Subjects
7 - 12	24	36	42
12 - 18	24	42	48

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772 **60 mg TID and up to 12 subjects randomised to GSK29827772 60 mg BID.** Using a Bayesian approach to determine the confidence interval (CI) around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in ~~20~~ **16** then the posterior distribution would be Beta (2, ~~20~~**16**), as outlined below in Figure 4.





Thus, we can be 95% certain that the true probability of the safety event lies between ~~0.01~~**2%** and ~~0.24~~**25%**.

For supportive information, the properties of the key secondary endpoint DAS28 have been considered.

Based on the estimate of variability (SD=1 from historical data) it is estimated that the lower and upper bounds of the 95% CI for the change from baseline in DAS28-CRP score will be within approximately ~~0.694~~**0.693** and ~~0.462~~**0.490** of the point estimate of GSK2982772 **60 mg TID** (n=~~20~~**18**) and placebo (n=~~10~~**8**).

Section 9.2.2 Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is **higher or** lower than **16** in the GSK2982772 group, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in **Table 5.**

Table 5 Sample Size Sensitivity

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
20	0	16.1%
20	1	23.8%
20	2	30.4%
18	0	17.6%
18	1	26.0%
18	2	33.1%
16	0	19.5%
16	1	28.7%
16	2	36.4%
14	**0**	**21.8%**
14	**1**	**31.9%**
14	**2**	**40.5%**
12	**0**	**24.7%**
12	**1**	**36.0%**
12	**2**	**45.4%**

Section 9.3.1 Analysis Populations

If 12 or more subjects are randomised to a BID regimen (i.e., ≥4 placebo and ≥8 GSK2982772 60 mg BID) then treatment received will take into account dosing frequency for GSK2982772, otherwise treatment will be irrespective of dosing frequency.

Section 9.3.2 Interim Analysis

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK ~~study physician~~**Project Physician Lead (PPL)**, the study statistician, the study pharmacokineticist, the PRR DPU Head, EDL and SRT Leader or designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data.

Section 11.0 References

GlaxoSmithKline Document Number 2014N204126_**02**. Investigator Brochure for GSK2982772. Report Date **27-JAN-2017**.

Section 12.1. Appendix 1 – Abbreviations and Trademarks

Anti-CCP	**Anti-Cyclic Citrullinated Peptide**
CARLOS	**Cartilage Loss Scoring System**
hCG	**Human Chorionic Gonadotropin**
LDL	**Low Density Lipoprotein**
MCV	**Mean Corpuscular Volume**
MDMA	**3,4-methylenedioxy-methamphetamine**
PPL	**Project Physician Lead**
SGOT	**Serum Glutamic Oxaloacetic Transaminase**
SGPT	**Serum Glutamic Pyruvic Transaminase**
TID	**Three times daily**
WOCP	**Women of Child Bearing Potential**

Section 12.4 Appendix 4 – Genetic Research

Genetic Research Objectives and Analyses

GSK2982772 is a novel first-in-class asset being introduced to patients with moderate to severe RA for the first time. Currently its mechanism of action is not fully characterised nor understood.

Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance. In addition, continuing research may identify other enzymes, transporters, proteins ore receptors that may be involved in response to GSK2982772. The genes that may code for these proteins may also be studied. Genome-wide scans involving a large number of polymorphic markers (e.g. single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene does not exist and/or the potential genetic effects are not well understood.

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

If applicable and genetic research is conducted, ~~A~~appropriate descriptive and/or statistical analysis methods will be used **to evaluate pharmacogenetic data in the context of the other clinical data**. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

12.7.2. Amendment 2 (14-JUL-2016) from Protocol Amendment 1 (25-MAY-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 02 incorporates addition of suicidal ideation and behaviour (SIB) withdrawal criteria.

Other minor protocol clarifications and administrative changes are also provided in this amendment.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Authors

Author (s): PPD

Author (s): PPD

MEDICAL MONITOR/SPONSOR INFORMATION

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	~~Tel:~~ PPD Mobile: PPD PPD Email: PPD PPD	Mobile: PP PPD PPD PPD	PPD	~~Pattern Recognition Receptor DPU,~~ UP4440 1250 S Collegeville, PA 19426 USA
Secondary Medical Monitor		Tel: PPD Mobile: PPD Email: PPD	Mobile: PPD PPD		Cytokine Chemokine DPU, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, UK
SAE contact information	Medical Monitor as above				

Section 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 medications for the treatment of RA as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or Haematologic stopping criteria (Section 5.4.5) are met.
- **The subject experiences any signs of suicidal ideation or behaviour (Section 7.3.7).**

Section 7.1 Time and Events Table

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact. **On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.**
6. All PRO assessments should be conducted before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. **If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).**
8. Subjects must take study medication twice a day approximately 12 hours apart. Exact time of dosing to be recorded in diary cards. **On Day 1, the first study dose will be administered at the site.** On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or at Early Withdrawal.
13. PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX must take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits must be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.
20. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (±3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.

Section 7.2 Screening and Critical Baseline Assessments

Medical/medication/**mental health and** family history, ECG and laboratory tests will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Section 7.3.7 Suicidal Risk Monitoring

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. ~~Consideration should be given to discontinuing GSK2982772 in s~~**All s**ubjects who experience signs of suicidal ideation or behaviour **must immediately be discontinued from study medication**.

Families and caregivers of subjects being treated with GSK2982772 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study Investigator.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening CSSRS' will be completed. **Assessments will be done at** ~~At~~ Days 43 (Week 6) and 85 (Week 12), the 'Since Last Visit CSSRS' will be completed. GSK Version 4.1 of both rating scales will be used.

Subjects who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their GP or appropriate psychiatric care **and be discontinued from study medication**. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 7.3.1 AE and SAE). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

12.7.3. Protocol Amendment 1 (25-MAY-2016) from the original protocol (01-APR-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 01 incorporates the addition of risk text for drug interaction with P-glycoprotein (Pgp) inhibitors and narrow therapeutic index (NTI) CYP3A4 substrates, and an updated list of prohibited medications.

Other minor protocol clarifications and administrative changes are also provided in this amendment.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Section 1 Protocol synopsis, Analysis, Paragraph 2

An ongoing review of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GlaxoSmithKline (GSK) individuals, some of whom are also members of the GSK study team **who are not involved in the day-to-day running of the study.**

Section 4.5 Dose Justification

It is anticipated that a human dose of 60 mg **BID** will produce area under the concentration-time curve ($AUC_{[0-24]}$) and maximum observed concentration (C_{max}) values of approximately 9 μg.h/mL and 1 μg/mL, respectively, which are approximately $1/6^{th}$ and $1/12^{th}$ of the gender-averaged AUC (48.4 μg.h/mL) and C_{max} (12.3 μg/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day.

Section 4.6.1 Risk Assessment

Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing ~~uptake of~~ **potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and** OAT3 **substrates** were completed. **To date, formal drug interaction studies in humans have not been performed with GSK2982772.** There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. MTX is an OAT3	**Subject Selections**: • **Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. See Section 6.11.2 for a comprehensive list of medications.** **Subject Monitoring:** • **Subjects' concomitant medication usage will be**

	substrate in which GSK2982772 could potentially impair the clearance of MTX. **There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772.** **GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772.** **See Section 4.3.6 of the GSK2982772 IB [GlaxoSmithKline Document 2014204126_01].**	**reviewed prior to inclusion and monitored throughout the study.** • **Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.** • PK sample collection to evaluate the potential interaction of GSK2982772 and MTX will be performed throughout the study. • Subjects should be monitored for potential effects of interaction between GSK2982772 and MTX. • Clinical laboratory results (e.g., liver function tests) are routinely being monitored throughout the study.

Section 5.2 Exclusion Criteria, Contraindications

CONTRAINDICATIONS
19. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
20. Received a live or attenuated vaccine within 30 days of randomization OR plan to receive a vaccination during the study until **5** half-lives (or 2 days) plus 30 days after receiving GSK2982772.
21. Contraindication to gadolinium contrast agent in accordance with local guidelines.
22. The subject has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer before the first dose of study medication, or plans to take part in another clinical trial at the same time as participating in this clinical trial.

Section 6.4 Blinding

This will be a double blind (sponsor unblinded) study and the following will apply:

- Sponsor unblinded refers only to the Data Review Committee, consisting of the GSK study physician, study statistician, study pharmacokineticist, **Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head,** Early Development Lead (EDL) and Safety Review Team (SRT) Leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this

review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.

Section 6.11.2 Amended Prohibited Medications and Non-Drug Therapies, Table 2 Prohibited Medications

Therapy	Time period
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	**4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112).**
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	**4 weeks prior to the first dose (Day1) until after the follow up visit (Day 112).**
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time.
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 ½ lives (whichever is longer) prior to first dose until

Therapy	**Time period**
	after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

Section 7.1 Time and Events Table

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------															----------X
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4]						X[4,20]						X	X[16]	

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
Study Treatment																
Randomisation		X														
Study medication (twice daily)[8]		X----------												----------X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, ~~Anti-CARP,~~ RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4]						X[4,20]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact.
6. All PRO assessments should be conducted before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist.
8. Subjects must take study medication twice a day approximately 12 hours apart. Exact time of dosing to be recorded in diary cards. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or at Early Withdrawal.
13. PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX must take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits must be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.
20. **A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (± 3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.**

Section 7.2 Screening and Critical Baseline Assessments

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

Section 7.3.4 Vital Signs

Vital signs will be measured in **a supine or** semi-supine position after approximately 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

Section 7.3.6 Clinical Safety Laboratory Assessments, Table 3 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology [1,2]</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [3]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose[4]</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>CRP</td><td>Triglycerides[4]</td><td>Total Cholesterol[4]</td><td>Fasting HDL cholesterol[4]</td></tr>
<tr><td>Fasting LDL cholesterol[4]</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravitypH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening and RoutineTests</td><td>• HIV 1 & 2
• Hepatitis B (HBsAg)
• Hepatitis B core antibody (HBcAb)
• Hepatitis C (Hep C antibody)
• QuantiFeron Gold Test
• T-spot (if QuantiFeron is indeterminant)
• FSH and estradiol (as needed in women of non-child bearing potential only)
• Urine hCG Pregnancy test (as needed for women of child bearing potential) [5]
• Serum hCG (as needed for women of child bearing potential) to be done at screening and if urine test positive at other time points in the</td></tr>
</table>

Laboratory Assessments	Parameters
	study. • Anti-dsDNA • Rheumatoid Factor • Anti-CCP • ~~Anti-CARP~~ • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula.

Section 9.3.2 Interim Analysis

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK study physician, the study statistician, the study pharmacokineticist, the **PRR DPU Head,** EDL and SRT Leader or designees on an ongoing basis.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with moderate to severe rheumatoid arthritis.

Compound Number: GSK2982772

Development Phase: II

Effective Date: 03-AUG-2017

Protocol Amendment Number: 04

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N251670_00	2016-APR-01	Original
2015N251670_01	2016-MAY-25	Amendment No. 1
Protocol Amendment 01 incorporates the addition of risk text for drug interaction with P-glycoprotein (Pgp) inhibitors and narrow therapeutic index (NTI) CYP3A4 substrates, an updated list of prohibited medications plus some minor protocol clarifications and administrative changes.		
2015N251670_02	2016-JUL-14	Amendment No. 2
Protocol Amendment 02 incorporates addition of suicidal ideation and behaviour (SIB) withdrawal criteria plus other minor protocol clarifications and administrative changes.		
2015N251670_03	2017-APR-20	Amendment No. 3
Change in dosing regimen from 60 mg BID to 60 mg TID, restrictions on JAK inhibitors, defined non-reproductive potential criteria in Exclusion 11, change to clinical laboratory criteria in Exclusion 23, addition of evaluation of joint space narrowing with MRI, flexibility in scheduling with MRI and synovial biopsy, some minor protocol clarifications and administrative changes.		
2015N251670_04	2017-AUG-03	Amendment No. 4
A country specific amendment for Germany which reinstates the clinical laboratory criteria in Exclusion 23 and Haematologic Stopping Criteria in Section 5.4.5 that was changed in Amendment 03.		

SPONSOR SIGNATORY

PPD

3rd AUGUST 2017.

Ramiro Castro-Santamaria, MD, MBA
Vice President, Head Unit Physician
ImmunoInflammation Therapy Area

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Telephone: PPD Email: PPD	Mobile: PPD	NA	GSK Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, UK
Secondary Medical Monitor		Mobile: PPD Email: PPD	Mobile: PPD	NA	1250 S. Collegeville Road, Collegeville, PA USA 19426
SAE contact information	Medical Monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

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

Regulatory Agency Identifying Number(s): EudraCT 2016-000912-13

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 203168

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

TABLE OF CONTENTS

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1. PROTOCOL SYNOPSIS FOR STUDY 203168

Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with moderate to severe rheumatoid arthritis (RA) who are currently being treated with disease modifying anti-rheumatic drugs (DMARDs).

The primary objective of this study has not changed with amendment 03; however the dosing regimen does change to GSK2982772 (60 mg three times daily for 84 days).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg three times daily for 84 days). In addition to the pharmacokinetics (PK), a number of experimental and clinical endpoints will be employed to obtain information on the pharmacodynamics (PD), and preliminary efficacy in subjects with active RA. Although no formal hypothesis will be tested, these endpoints will enable a broader understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in RA, by making full use of the information obtained from each subject enrolled.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8 and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).

Objectives	Endpoints

• To investigate the effect of 60 mg three times daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Magnetic Resonance Imaging (MRI) parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, bone oedema and joint space narrowing as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, the RAMRIQ (Rheumatoid arthritis MRI quantitative) scoring system, the modified CARLOS (Cartilage Loss Scoring System) and additional exploratory endpoints as data permit.
	• Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:
	  • Exchange rate (K^{trans})
	  • Interstitial volume (V_e)
	  • Plasma volume (V_p)
	  • Initial rate of enhancement (IRE)
	  • Maximal signal intensity enhancement (ME)
	  • Joint volume
	  • Enhancing volume

• To investigate the effect of 60 mg three times daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg three times daily dosing of GSK2982772 on methotrexate (MTX) concentrations.	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue from subjects with moderate to severe	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells,

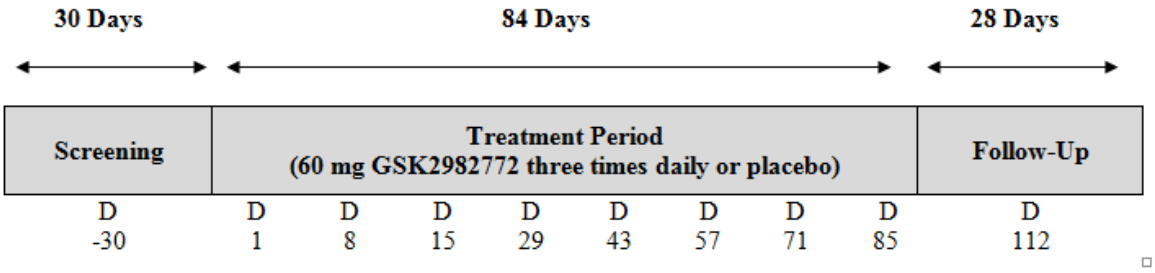
Objectives	Endpoints
Rheumatoid Arthritis.	and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.
• To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and synovial biopsy tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit: • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue. • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg three times daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood subjects with active moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

Overall Design

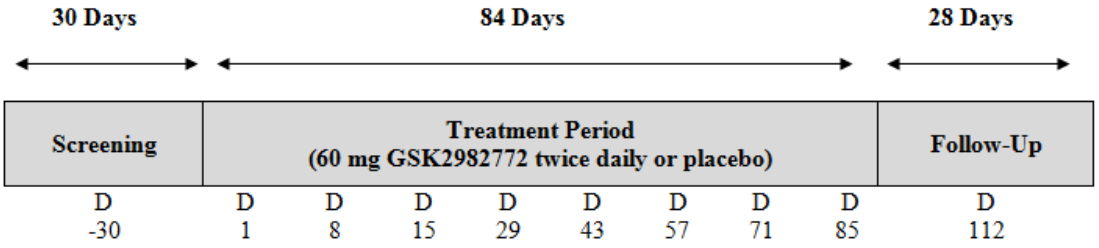
This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA. The study design schematic is depicted in Figure 1 below.

Figure 1 Study Overview

Amendment 03:



Prior to amendment 03:



Key assessments:
Safety assessments, PK samples, DAS28-CRP, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom and Impact Diary, HAQ-DI assessments, MRI, PD samples

Treatment Arms and Duration

Each subject will participate in the study for approximately 20 weeks. This includes a screening period of up to 30 days, an 84 day (12 week) treatment period, and a 28 day follow-up period after the last dose.

Within 30 days of the screening visit (defined as day of consent signing), subjects who are eligible will enter the treatment period and start treatment (or dosing) on Day 1.

The Follow-up Period is 28 days (4 weeks) long. All visits and assessments are detailed in Section 7.1.

Subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg three times daily (TID)

Placebo three times daily (TID)

Prior to amendment 03 being effective in each country, subjects have been randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg two times daily (BID)

Placebo two times daily (BID)

Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 24 subjects with moderate to severe RA are randomised into the study on a TID regimen. Prior to protocol amendment 03 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Should the overall drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to an overall total maximum of 48) into the study at the discretion of the Sponsor.

Analysis

The safety and tolerability of GSK2982772 following 12 weeks of treatment will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead electrocardiogram (ECG) monitoring.

Ongoing reviews of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GlaxoSmithKline (GSK) individuals, some of who are also members of the GSK study team who are not involved with the day-to-day running of the study. The primary purpose of these reviews will be to monitor target engagement, inflammatory markers and Disease activity score for 28 different joints with (CRP) value (DAS28-CRP) for futility and internal decision making. A data review charter will outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted during the study, when an appropriate number of subjects have completed 12 weeks of treatment or on the request of the DRC. The purpose of this interim will be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in DAS28-CRP

will be statistically analysed using a Mixed-effect Model Repeat Measurements (MMRM) comparing GSK2982772 with placebo at each time point.

The relationship between each of the mechanistic endpoints and also with the clinical endpoints may also be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g DAS28-CRP). In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain change in DAS28-CRP (i.e., comparatory rate), based on the data that we have observed in the study. Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

2. INTRODUCTION

2.1. Study Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with moderate to severe rheumatoid arthritis (RA) who are currently being treated with disease modifying anti-rheumatic drugs (DMARDs). All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication type and dose is stable throughout the study.

The primary objective of this study has not changed with amendment 03; however the dosing regimen does change to GSK2982772 (60 mg three times daily for 84 days).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg three times daily for 84 days). In addition, a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy in subjects with moderate to severe RA.

2.2. Brief Background

RIP1 is a member of the receptor-interacting Serine/Threonine kinase family containing an amino-terminal kinase domain, an intermediate domain and a carboxy-terminal death domain. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including tumor necrosis factor (TNF) family cytokines, ligands for toll-like receptor (TLR) 3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis

[Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008, Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_02]. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and NF-kB-signalling [Ofengeim, 2013, Humphries, 2015]. With this, an inhibitor of RIP1 kinase activity with GSK2982772 may fill a unique niche in the treatment of inflammatory conditions through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a debilitating, progressive polyarthritis that typically affects the small joints of the hands and feet [Vasanthi, 2007]. TNF is known to be one of the key cytokines that drives inflammation in RA [Choy, 2001]. In animal models, transgenic mice that chronically over express low levels of TNF develop a spontaneous polyarthritis that resembles RA in humans [Keffer, 1991] and blockade of NFκB activation results in the development of a spontaneous murine polyarthritis that is RIP1-dependent [Berger, 2014]. In RA patients, TNF is detected in high concentrations in both blood and synovial fluid, and expression of TNF and its signalling intermediates, including RIP1, have been shown to be constitutively increased in PBMCs from RA subjects compared to healthy controls [Raghav, 2006].

Synthetic disease modifying antirheumatic drugs (DMARDs) including nonsteroidal anti-inflammatory drugs, steroids, methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide, are often used alone or in combination in moderate to severe RA; however, most DMARDs do not significantly impact disease progression, and may be hampered by poor side effect profiles. Recently, tofacitinib, an oral small molecule inhibitor of JAK, was approved for moderate to severe RA, but its long term safety is still unknown. TNF antagonists are used in the treatment of patients with moderate-severe disease who have not responded or who have intolerance to traditional DMARDs. While studies have shown that they can improve symptoms and slow the progression of joint damage in many patients [Agarwal, 2011], only half of RA patients achieve American College of Rheumatology (ACR) 50 criteria, and many become refractory to anti-TNF treatments after several years. In addition to the association with increased rates of opportunistic infections across all indications, anti-TNF therapy in RA is linked to lupus-like syndrome and increased rates of demyelinating disease. Other biologic therapies which inhibit T cell activation (abatacept) or lead to selective B cell depletion (rituximab) have shown clinical efficacy in anti-TNF refractory patients, although both carry potential risks for serious infection. Therefore, there remains a high unmet need for safe and tolerable therapies that lead to improved rates of clinical remission and increased physical function in patients with moderate to severe RA.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8, and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in MRI parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, bone oedema and joint space narrowing as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, the RAMRIQ (rheumatoid arthritis MRI quantitative) scoring system, the modified CARLOS (Cartilage Loss Scoring System) and additional exploratory endpoints as data permit. • Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist: • Exchange rate (K^{trans})

Objectives	Endpoints
	• Interstitial volume (V_e) • Plasma volume (V_p) • Initial rate of enhancement (IRE) • Maximal signal intensity enhancement (ME) • Joint volume • Enhancing volume
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg three times daily dosing of GSK2982772 on methotrexate (MTX) concentrations	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.

• To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit:
	  • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue.
	  • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.

Objectives	Endpoints
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg three times daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

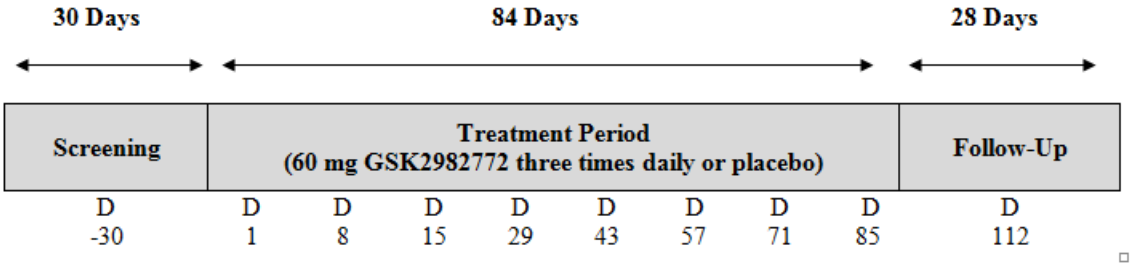
4. STUDY DESIGN

4.1. Overall Design

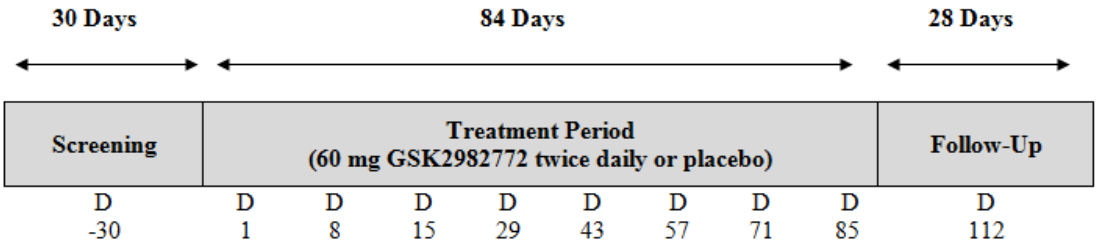
This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA. The study design schematic is depicted in Figure 2 below.

Figure 2 Study Overview

Amendment 03:



Prior to amendment 03:



Key assessments:
Safety assessments, PK samples, DAS28-CRP, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom and Impact Diary, HAQ-DI assessments, MRI, PD samples

4.2. Treatment Arms and Duration

It is anticipated that the total duration of participation in the study will be approximately 20 weeks from screening to the last study visit.

4.2.1. Screening

Within 30 days of the screening visit (defined as day of consent signing), subjects who are eligible will enter the treatment period and start treatment (or dosing) on Day 1.

4.2.2. Treatment Period

Subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally three times daily (approximately 8 hours apart) for 84 days (12 weeks). Subjects that were randomised prior to protocol amendment 03 being approved in each country were randomly assigned to either GSK2982772 60 mg or placebo orally two times daily (approximately 12 hours apart) for 84 days (12 weeks).

Further guidance and information for study treatment and dosing are provided in the Study Reference Manual (SRM).

During the 84 day (12 week) treatment period, subjects will attend the clinical site for visits on Days 1, 8, 15, 29, 43, 57, 71 and 85. At specific visits, subjects must not take study treatment prior to their scheduled visit (see Section 7.1). On Days 22, 36, 50, 64 and 78, each subject will be contacted by telephone and asked about their general health, study medication compliance and diary card completion. Subjects will be given a diary card at each of the visits on which they will be instructed to record their daily study medication and concomitant medication taken and any adverse events.

4.2.3. Follow-up Period

After the Treatment Period, the subject will enter the Follow-up Period which lasts for 28 days post the last administration of study medication, in order to complete follow-up assessments per the Time and Events Table (see Section 7.1).

4.3. Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 24 subjects with moderate to severe RA are randomised into the study on a TID regimen. Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Should the overall drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to an overall maximum of 48) into the study at the discretion of the Sponsor.

4.4. Design Justification

As this is the first trial of GSK2982772 in subjects with RA, the primary endpoint is the safety and tolerability of GSK2982772. In addition, this study will include assessments of target engagement and downstream PD effects of GSK2982772, to understand whether GSK2982772 is inhibiting the pathway of interest in this disease.

The 12 week duration of treatment is based on review of previous proof of mechanism and proof of concept studies in RA and is limited by the supporting 13 week toxicology studies. It is expected that an effective therapy should cause group level changes in the mechanistic parameters by the 12 week time point.

The subjects will be randomised in a 2:1 ratio to GSK2982772 60 mg three times daily (TID) and placebo respectively. The primary objective of this study is to assess safety and tolerability, and assessment of this is most valuable in a placebo controlled study.

The placebo group was also deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication and dose is stable throughout the study.

4.5. Dose Justification

The initial selection of the 60 mg BID dose being tested in this study is based on the safety, PK, and PD data from the First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was initially selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2h). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose was predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects will have >90% target engagement in blood at C_{min} using a novel in-house ex-vivo PD/target engagement assay based solely on the TNF pathway which is believed to be a key component of the RIP1 pathway.

However, based on final PK/PD modelling from the full repeat dose part of the Study 200975 (up to 120 mg BID), a 60 mg BID dose is now predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >85% target engagement at C_{min}. This is lower than our target of achieving >90% target engagement in at least 90% of subjects at C_{min}. Therefore, a 60 mg TID cohort is now being proposed.

The C_{min} values at 60 mg TID are predicted to be approximately 3.5 fold higher than for 60 mg BID. Using the final PK/PD, a 60 mg TID dose is predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >96% target engagement at C_{min}. No data are currently available about the distribution of GSK2892772 into the synovium. Based on data in non-steroidal anti-inflammatory drugs (NSAIDs), the synovial fluid concentrations fluctuate to a much lesser extent than those in plasma [Netter, 1989]. Peak drug concentrations are generally lower in synovial fluid but are similar to plasma at later time points. Assuming the same is true for GSK2982772, a 60 mg TID dose should provide similar RIP1 target engagement at the site of action as predicted in blood.

In addition, because of the short half-life, a modified release formulation is now being developed with the aim to provide a once daily dosing regimen. By increasing the frequency of dosing to three times daily (TID) with the current immediate release formulation, this will more closely match the PK, safety and efficacy profile of a preferred once daily modified release formulation.

The safety of increasing the dose frequency to 60 mg TID is justified based on nonclinical safety findings to date with GSK2982772. It is anticipated that a human dose of 60 mg TID (180 mg/day) will produce $AUC_{(0-24)}$ and C_{max} values of approximately 9.9 ug.h/mL and 0.8 ug/mL, respectively, which are approximately $1/5^{th}$ and $1/15^{th}$ of the

gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

As of 03 Apr 2017, a total of approximately 93 subjects across 4 clinical studies have been randomised to receive GSK2982772. In Study 200975, GSK2982772 administered up to 120 mg BID for 14 days and was well tolerated and no safety concerns were identified. A total of 9 subjects had received 120 mg BID in that study. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. In the ongoing Phase 2a studies in Psoriasis [(PsO); Study 203167] and Rheumatoid Arthritis [(RA); Study 203168], a total of 26 subjects have been randomised to GSK2982772 60 mg BID. GSK2982772 was well tolerated and no drug-related SAEs have been reported. In Study 203167, there was a death of a 19 year old male subject due to an accidental overdose with 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the IB [GlaxoSmithKline Document Number 2014N204126_02]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2982772		
Central Nervous System (CNS) effects	**Non-clinical data**: In the 4-week GLP toxicology study, CNS findings were observed in 4/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance, and decreased activity. The clinical relevance of these findings in humans is not known. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical data**: A First Time in Human (FTiH) study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date. See Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_02]. No drug-associated CNS adverse events were identified and no Serious Adverse Effects (SAEs) were reported.	**Subject Selction**: • Subjects with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening. **Subject Monitoring**: • Subjects will be monitored for standard CNS-related adverse events.
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, HIV, Hepatitis B and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	other immunomodulating drugs or corticosteroids. **Clinical data**: In the FTiH study, no SAEs were reported. One subject experienced an Adverse Effect (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded Investigator determined this to be potentially drug-related.	C, and excluded from the study if positive. **Subject Monitoring**: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 5.4.1).
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in subjects with RA.
Respiratory	**Non-clinical data**: In the single dose Safety Cardiovascular (CV) and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related adverse events. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	ventilation (minute volume) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02]. **Clinical data**: In the FTiH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related adverse events were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based upon pre-clinical studies. **Clinical data**: In the FTiH study, there have been some reports of lethargy, abnormal dreams, and depressed mood. No events of suicidal ideation or behaviour or changes in behaviour were reported.	**Subject Selection**: • Subjects with a current history of suicidal ideation and behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel using the (Columbia Suicide Severity Rating Scale) C-SSRS in all subjects. See Section 7.3.7.
Reproductive toxicity	**Non-clinical data:** In an early rat embryofetal development study, there was no maternal or developmental toxicity at doses ≤200 mg/kg/day. In a rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection**: • Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 30days (females) and 90 days (males) after the last administration of study drug (Appendix 6).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and OAT3 substrates were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. MTX is an OAT3 substrate in which GSK2982772 could potentially impair the clearance of MTX. There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772. GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp	**Subject Selections**: • Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. See Section 6.11.2 for a comprehensive list of medications. **Subject Monitoring:** • Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. • Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications. • PK sample collection to evaluate the potential interaction of GSK2982772 and MTX will be performed throughout the study. • Subjects should be monitored for potential effects of interaction between GSK2982772 and MTX. • Clinical laboratory results (e.g., liver function tests)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	inhibitors could increase circulating levels of GSK2982772. See Section 4.3.6 of the GSK2982772 IB [GlaxoSmithKline Document 2014N204126_02].	are routinely being monitored throughout the study.
Study Procedures		
Synovial Joint Biopsy	Potential risks of the procedure include discomfort, infection or bleeding. **Note**: Synovial biopsies are optional and not required on all subjects.	**Subject Selection:** • Subjects with known allergy to lidocaine or other local anaesthetics will not be included in the biopsy portion of the study. • Subjects with a platelet count ≤100 x 10^9/L will be excluded from participation. **Subject Management**: • The biopsies will be performed under ultrasound or arthroscopic guidance. Subjects will be given instructions for aftercare and contact information should there be any adverse reactions after the procedure. • Biopsy site healing will be monitored during the study as part of AE safety review.
Gadolinium (Gd) containing MRI contrast agents	**Non-clinical data**: Animal studies have shown reproductive toxicity of gadolinium (Gd)-containing MRI contrast agents at repeated high doses. **Clinical data**: Use of MRI contrast agents in subjects with severely impaired rental function (GFR<30mL/minute) has been associated with Nephrogenic Systemic Fibrosis (NSF). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed	**Subject Selection:** • Pregnant or lactating females will be excluded from taking part in the study. • Subjects with impaired renal function (GFR<60mL/minute) are excluded by the eligibility criteria. • Subjects with history of sensitivity to Gd-containing contrast agents will be excluded from the study. The MRI procedure will be conducted under the supervision of trained and qualified clinical staff that is trained to appropriately manage an allergic reaction. • Sites will be responsible for following any additional

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	against the risks. Gadolinium (Gd) contrast agents can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory, or cutaneous manifestations, and ranging to severe reactions including shock. In general, subjects with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions. The risk of hypersensitivity reactions may be higher in cases of: • Previous reaction to contrast media • History of bronchial asthma • History of allergic disorders Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely observed.	safety information for the specific Gd contrast agent used at their site and not enroll subjects if contraindicated. **Subject Monitoring and Management**: • MRI contrast at a dose less than or equal to 0.1 mmol/kg per imagining session at baseline and Days 43 and 85 will be used in the MRI protocol. • Effective contraception is required during the study, and pregnancy testing will be performed regularly throughout the study and prior to dosing in females of child bearing potential.
Other		
Exposure to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner.	**Subject Selection:** • All participants will be screened according to local hospital criteria and study inclusion/exclusion before entering the MRI scanner to ensure they are able to have the MRI conducted. Subjects with non-magnetic resonance compatible metal implants or implantable electronic devices (e.g., pacemaker, defibrillator) will not be included in this study.

4.6.2. Benefit Assessment

There are additional treatment options available for subjects who have an inadequate response to current therapies for RA. It is possible that treatment with GSK2982772 may be effective in the treatment of RA, as the FTiH study demonstrated that the drug engaged with the target and produced *ex vivo* PD effects in suppression of RIP1-dependent cytokines MIP1α and MIP1β [GlaxoSmithKline Document Number 2014N204126_02]. There will be limited direct benefit to the subject through their contribution to the process of developing new therapies in an area of unmet need.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded to patients with RA by contributing to the understanding of the disease and the development of new therapies for patients with these conditions in the future.

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 (IP) or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number 2014N204126_02].

In addition, Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including vaccinations for influenza and pneumococcus, in subjects with RA.

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

5.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects that do not have any medical conditions, other than moderate to severe RA that in the opinion of the Investigator put the subject at unacceptable risk or interfere with study assessments or integrity of the data. These medical conditions should be

stable at the time of screening and are expected to remain stable for the duration of the study.

3. Subject has had a confirmed diagnosis of rheumatoid arthritis according to the revised 2010 American College of Rheumatology/European League Against Rheumatism ACR-EULAR classification criteria.
4. Disease duration of ≥12 weeks (time from onset of patient-reported symptoms of either pain or stiffness or swelling in hands, feet or wrists) at screening.
5. Swollen joint count of ≥4 (28-joint count) and tender joint count ≥4 (28-joint count) at screening.
6. Subject has a DAS28 CRP disease activity score of ≥3.2 and CRP ≥5.0 mg/L (≥4.76 nmol/L) at screening.
7. Subject must have received at least 12 weeks of non-biologic DMARD monotherapy or methotrexate (MTX)/DMARD combination therapy prior to screening AND must be on stable dose throughout the study.
8. Subject is naive to any biological therapies for RA

   OR

   Subject may have had previous exposure to a single anti-TNF biologic agent which was discontinued for reasons other than primary non-response more than 8 weeks (or 5 half-lives whichever is longer) from first dose. **Note: Exposure to a single anti-TNF is not required in addition to Inclusion #7 above.**
9. For subjects who have consented to synovial joint biopsy:
   a. Subject has an involved knee, wrist, or ankle suitable for biopsy, as assessed by a rheumatologist at screening.

WEIGHT
10. A body mass index (BMI) within range of 18.5 - 35 kg/m^2 (inclusive) at screening.

SEX
11. Male and female subjects **Males:** Male subjects with female partners of child bearing potential must comply with the following contraception requirements in Appendix 6. **Females**: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation

- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

- Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods (see Appendix 6) if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 6) from 30 days prior to the first dose of study medication and until at least 30 days after the last dose of study medication and completion of the follow-up visit.

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

INFORMED CONSENT
12. 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. Subject with a positive anti-double stranded deoxyribonucleic acid (DNA [anti-dsDNA]) and confirmed diagnosis of systemic lupus erythematosus (SLE). 2. Subject with current history of Suicidal Ideation Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide. 3. An active infection, or a history of infections as follows: • Hospitalisation for treatment of infection within 60 days before first dose (Day 1). • Currently on any suppressive therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and

atypical mycobacteria).

- Use of parenteral (IV or intramuscular) antibiotics (antibacterials, antivirals, antifungals, or antiparasitic agents) for an infection within 60 days before first dose.
- A history of opportunistic infections within 1 year of screening (e.g. pneumocystis jirovecii, CMV pneumonitis, aspergillosis). This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or recurrent nature.
- Recurrent or chronic infection or other active infection that, in the opinion of the Investigator might cause this study to be detrimental to the patient.
- History of TB, irrespective of treatment status.
- A positive diagnostic TB test at screening defined as a positive QuantiFERON-TB Gold test or T-spot test. In cases where the QuantiFERON or T-spot test is indeterminate, the subject may have the test repeated once, but they will not be eligible for the study unless the second test is negative. In cases where the QuantiFERON or T-spot test is positive, but a locally-read follow up chest x-ray, shows no evidence of current or previous pulmonary tuberculosis, the subject may be eligible for the study at the discretion of the Investigator and GSK Medical Monitor.

4. QTc >450msec or QTc >480msec for subjects with bundle branch block at screening.

   The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual over read.

   The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined and documented prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
5. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
6. Current active or chronic history of liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. Current or history of renal disease or estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 mL/min/1.73m^2 at screening.
8. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
9. A major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
10. Any planned surgical procedures including surgical joint procedures (e.g., intra-articular, tendon sheath, or bursal corticosteroid injections) during the study.
11. A history of malignant neoplasm within the last 5 years, except for adequately treated

non-metastatic cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix that has been fully treated and shows no evidence of recurrence.

12. Has undergone surgery including synovectomy or arthroplasty on the joint chosen for biopsy and/or magnetic resonance imaging (MRI).
13. The subject has a history of any other joint disease other than RA at the knee, wrist or ankle joint chosen for biopsy and/or MRI (e.g., gout, pseudogout, osteoarthritis).
14. Has undergone intra-articular corticosteroid injection, arthrocentesis or synovial biopsy on any joint within 6 weeks of screening.
15. A known allergy to lidocaine or other local anaesthetics (**Note**: only applies to subjects who consent for synovial biopsy procedures).
16. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but are not limited to:
    - Intracranial aneurysm clips (except Sugita) or other metallic objects,
    - History of intra-orbital metal fragments that have not been removed by a medical professional.
    - Pacemakers or other implanted cardiac rhythm management devices and non-MR compatible heart valves,
    - Inner ear implants,
    - History of claustrophobia which may impact participation.

CONCOMITANT MEDICATIONS
17. The subject has received treatment with the therapies listed in Section 6.11.2, or changes to those treatments, within the prescribed timeframe. If in doubt, or the therapy is not listed please consult with the medical monitor. • 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
18. History of alcohol or drug abuse that would interfere with the ability to comply with the study.

CONTRAINDICATIONS
19. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation. 20. Received a live or attenuated vaccine within 30 days of randomization OR plan to receive a vaccination during the study until 5 half-lives (or 2 days) plus 30 days after receiving GSK2982772. 21. Contraindication to gadolinium contrast agent in accordance with local guidelines. 22. The subject has participated in a clinical trial and has received an investigational

product within 30 days or 5 half-lives, whichever is longer before the first dose of study medication, or plans to take part in another clinical trial at the same time as participating in this clinical trial.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
23. Haemoglobin <9 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L); platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at screening. *For subjects recruited in Germany: Haemoglobin <11 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L); platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at screening.* 24. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. As potential for and magnitude of immunosuppression with this compound is unknown, subjects with presence of hepatitis B core antibody (HBcAb) should be excluded. 25. A positive serology for human immunodeficiency virus (HIV) 1 or 2 at screening. 26. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months. 27. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dose.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5).

Subjects who do not qualify to participate in the study due to a screening laboratory value or ECG abnormality can repeat the test once within the original screening window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

Subjects can be re-screened only on approval of the GSK Medical Monitor and only once. Re-screening is allowed when a subject failed inclusion/exclusion criteria or some other screening condition initially, but the Investigator believes there is a reasonable probability that the subject would be eligible if re-screened.

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 Case Report Form (CRF).

- The Sponsor's request, for reasons such as significant protocol deviations or subject safety concern (and after discussion with the Investigator).
- If a subject is withdrawn from study treatment, this subject is also considered to be withdrawn from the study.
- Study is terminated by the Sponsor.

If a subject is withdrawn, the Sponsor may decide to replace that subject and this will be done through the Interactive Response Technology System (IRTS).

If a subject chooses to withdraw from the study after dosing then the Investigator must make every effort to complete the follow-up assessments detailed in the Time and Events Table (Section 7.1).

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

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

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 medications for the treatment of RA as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or Haematologic stopping criteria (Section 5.4.5) are met.

- The subject experiences any signs of suicidal ideation or behaviour (Section 7.3.7).

5.4.2. Group Safety Stopping Criteria

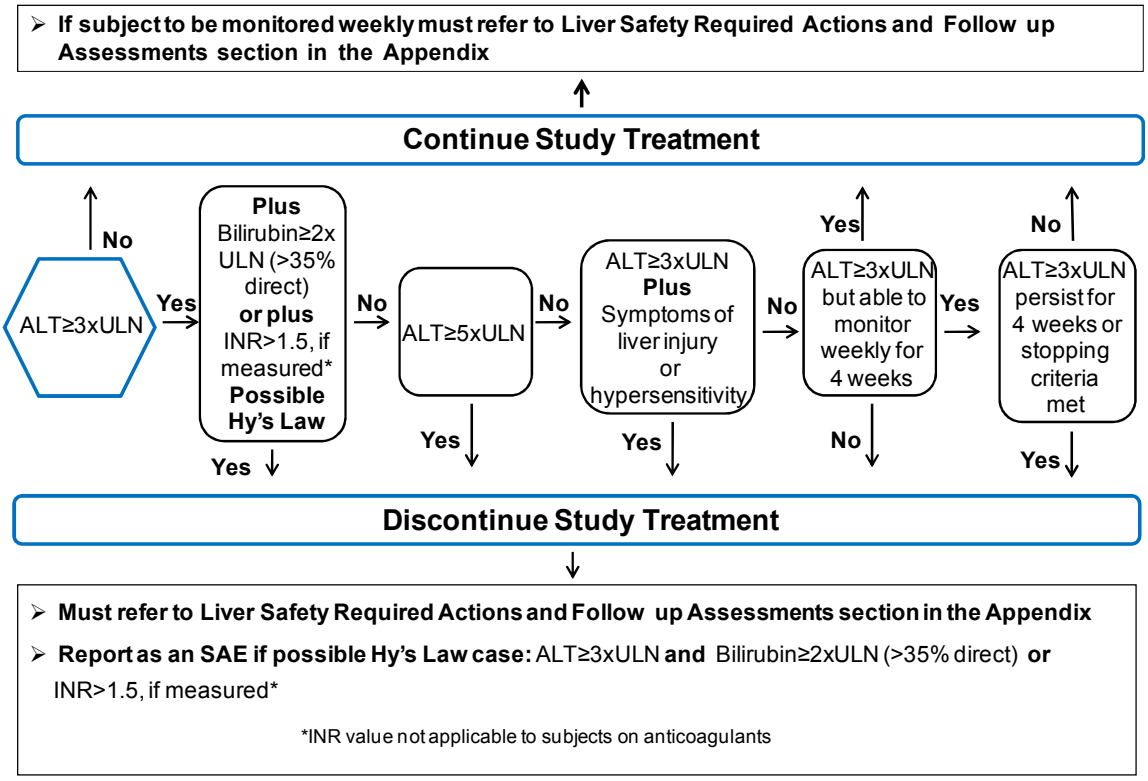
In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subjects will be regularly reviewed by the Sponsor Safety Review Team (SRT) in order to ensure appropriate subject safety. Any changes to the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

5.4.3. 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

Figure 3 Phase II Liver Chemistry Stopping Criteria – Liver Stopping Events Algorithm



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

5.4.3.1. 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.

5.4.4. QTc Stopping Criteria

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

- 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 decision to withdraw a subject will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.4.5. Haematologic Stopping Criteria

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

- Haemoglobin - an absolute decrease of ≥2 g/dL from baseline (pre-dose Day 1). *For subjects enrolled in Germany: Haemoglobin <9 g/dL (5.58 mmol/L) or an absolute decrease of ≥2 g/dL from baseline (pre-dose Day 1).*
- Platelets $<50 \times 10^9$/L

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 study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions (with amendment 03):	Take TWO tablets three times a day as directed by your physician	Take TWO tablets three times a day as directed by your physician
Dosing instructions (prior to amendment 03):	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Physical description:	White to almost white, round, film coated tablet	White to almost white, round, film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

6.2. Treatment Assignment

At Screening a unique Subject Number will be assigned to any subject who has signed a consent form. The unique Subject Number will be used to identify individual subjects during the course of the study. Any subject that is re-screened outside of the allowed screening window at the approval of the GSK Medical Monitor, must be assigned a new unique Subject Number.

Subjects who meet screening eligibility criteria will be randomised to a treatment group through an Interactive Response Technology System (IRTS). The IRTS will confirm the subject's CRF number (Subject Number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other subject in the study.

Therefore, the randomisation is centrally controlled by the IRTS.

Subjects will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio.

6.3. Planned Dose Adjustments

No dose adjustments are allowed.

6.4. Blinding

This will be a double blind (sponsor unblinded) study and the following will apply:

- Sponsor unblinded refers only to the Data Review Committee, consisting of the GSK Project Physician Lead (PPL), study statistician, study pharmacokineticist, Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head, Early Development Lead (EDL) and Safety Review Team (SRT) Leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.
- The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator. Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject to his/her study staff or GSK, 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.
- A subject will be withdrawn if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (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.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing.

When subjects self-administer study treatment(s) at home, compliance with GSK2982772 and placebo will be assessed and documented through the review of the subject's diary card and querying the subject during the site visits. A record of the number of GSK2982772 or placebo tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

Subjects will be given instructions on compliance and treatment with MTX (if applicable). The date, time and total weekly dose will be recorded in the study diary cards and the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 >180 mg daily will be considered an overdose. GSK does not recommend specific treatment for an overdose. The Investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

In the event of an overdose, the Investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) for at least 48 hours following the last dose of GSK2982772.
3. Obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document all details of the overdose 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

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

Subjects will not receive any additional treatment from GSK after completion of the study because the 12 week duration of treatment is limited by the supporting 13 week toxicology studies.

6.10. Lifestyle and/or Dietary Restrictions

- Subjects must adhere to the contraceptive requirements listed in Appendix 6.

6.10.1. Activity

- Subjects will abstain from strenuous exercise more than their normal routine for 48 hours prior to each blood collection for clinical laboratory tests.
- Subjects who have consented to synovial biopsies will abstain from strenuous exercise for 24 hours after synovial biopsy procedures.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Selected medications for the treatment of RA may be taken, with specific requirements listed in Table 1, and as long as they are not prohibited (Section 6.11.2). All concomitant medications taken during the study will be recorded in the source document and CRF. The minimum requirement is that drug name and dates of administration are recorded.

Table 1 Specific Requirements for Permitted Medications During the Study

Drug	Requirement
Methotrexate	Stable dose regimen (up to 25 mg/week) for at least 12 weeks prior to screening and remain on this dose throughout the study (unless dose must be reduced because of a safety concern). MTX should ideally be taken on the same day of week and at approximately the same time of day throughout the study.
Sulfasalazine	Stable dose regimen for at least 12 weeks prior to screening and throughout the study.
Hydoxychloroquine or cholorquinine	Stable dose for at least 12 weeks prior to screening and throughout the study.
Leflunomide	Stable dose for at least 12 weeks prior to screening and throughout the study.
Folate supplements (minimum of 5 mg/week)	If a subject is on folate supplements with MTX treatment, they must be on a stable dose regimen for at least 4 weeks prior to randomization and throughout the study.
Other oral anti-rheumatic therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticords (e.g., prednisolone ≤ 10 mg /day. See Appendix 3 for equivalent doses).	Stable dose regimen for at least 4 weeks prior to screening and throughout the study (unless reduction required due to adverse effects). Omit dose on the morning prior to study visits until after joint assessments.

6.11.2. Prohibited Medications and Non-Drug Therapies

Table 2 lists prohibited medications for defined periods of time before and during the study until after the follow up visit.

Subjects who start prohibited medications or therapies as a treatment for RA or other reasons during the study will be withdrawn from study treatment for safety reasons. If in any doubt, Investigators are advised to discuss medications with the medical monitor.

Table 2 Prohibited Medications

Therapy	Time period
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
Janus Kinase (JAK) Inhibitors	4 weeks prior to screening until after the follow up visit (Day 112).
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112).
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	4 weeks prior to the first dose (Day 1) until after the follow up visit (Day 112).
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time.
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 half lives (whichever is longer) prior to first dose until after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered

Therapy	Time period
	whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM and laboratory manual. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

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

- At study visits, the Patient Reported Outcomes (PROs) should be completed prior to any other study assessments.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak 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.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- 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.

7.1. Time and Events Table

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------X															
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4, 20]						X[4,21]						X[22]	X[16]	

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Study Treatment																
Randomisation		X														
Study medication (three times daily)[8]		X----------												----------X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4,20]						X[4,21]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact. On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.
6. All PRO assessments should be conducted on site before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).
8. Subjects must take study medication three times a day approximately 8 hours apart. Exact time of dosing to be recorded in diary cards. On Day 1, the first study dose will be administered at the site. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71. When clinical laboratory samples are taken on the same day as the MRI, the samples should be taken first prior to the administration of the contrast fluid with MRI. If this is not feasible (i.e. MRI is performed first), it is recommended that a separate IV catheter or straight venipuncture be performed in the *opposite* arm to where the MRI contrast fluid was administered.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours. A trough PK sample will be taken on Day 85 or at Early Withdrawal.
13. Only applicable if subjects are on MTX: PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX should ideally take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits should ideally be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit. A window allowance of $\pm$ 3 days of Early Withdrawal visit is allowed to perform the MRI.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days ($\pm$3 days) after the last dose of study medication.
20. MRI (and if applicable; a biopsy) may be performed during the screening window as an additional visit (if required) up to 7 days before Day 1 to allow sites flexibility in scheduling. The MRI must be completed prior to synovial biopsy (if performed on the same joint). The site should be reasonably confident that the subject has fully qualified for the study (e.g., screening clinical labs, vital signs, physical examination, etc.) before the MRI (and if applicable: a biopsy) is/are performed.

21. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (±3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.
22. For MRI performed on day 85, a visit window of up to 2 days after is allowed in order to perform the MRI.

7.2. Screening and Critical Baseline Assessments

After written informed consent, screening assessments will be performed as outlined in the Time and Events Table (Section 7.1).

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

Medical/medication/mental health and family history, ECG and laboratory tests will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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

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

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The Investigator will be responsible for determining the clinical significance of any results that fall outside of the laboratory normal ranges.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT), which will include 203168 study team members, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

7.3.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 5.

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the time points specified in the Time and Events Table (Section 7.1).

- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.3.1.2. Method of Detecting AEs and SAEs

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

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

7.3.1.3. 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 stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the 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.

7.3.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.3.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 30 up to 90 days (as applicable) after the last dose.
- If a pregnancy is reported within 30 days (90 days in partners) after the last dose then the Investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the head, eyes, ears, nose, throat, skin, thyroid, joint, lymph nodes, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded at the first physical examination.
- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.3.4. Vital Signs

- Vital signs will be measured in a supine or semi-supine position after approximately 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

7.3.5. Electrocardiogram (ECG)

- Triplicate12-lead ECGs will be obtained at screening and single 12-lead ECGs obtained at every time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F or B) intervals. A manual over read is also allowed. Refer to Section 5.4.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period.
- ECG to be measured in a semi-supine position after approximately 5 minutes rest.

7.3.6. Clinical Safety Laboratory Assessments

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

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

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

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

- Haematology, platelets and coagulation sample if they are required to be taken closer to the biopsies (as per local practices) than specified in Section 5.4.5.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology [1,2]	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [3]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose[4]	Calcium	Alkaline phosphatise	Albumin
	CRP	Triglycerides[4]	Total Cholesterol[4]	Fasting HDL cholesterol[4]
	Fasting LDL cholesterol[4]			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening and RoutineTests	• HIV 1 & 2 • Hepatitis B (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis C (Hep C antibody) • QuantiFeron Gold Test • T-spot (if QuantiFeron is indeterminant) • FSH and estradiol (as needed in women of non-child bearing potential only) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [5] • Serum hCG (as needed for women of child bearing potential) to be done at screening and if urine test positive at other time points in the study. • Anti-dsDNA • Rheumatoid Factor • Anti-CCP • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula.			

Footnotes:

1. The subject's CBC results from the previous scheduled visit should be checked prior to the synovial biopsy procedures according to local practices and may be repeated at the discretion of the investigator.

2. Details of Haematologic Stopping Criteria are given in Section 5.4.5.
3. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.3 and Appendix 2.
4. No fasting required. Any abnormal result for glucose or lipids (non-fasted) may be repeated at the discretion of the Investigator.
5. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

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

7.3.7. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with RA. Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. Study medication must be immediately discontinued in all subjects who experience signs of suicidal ideation or behaviour.

Families and caregivers of subjects being treated with GSK2982772 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study Investigator.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening CSSRS' will be completed. Assessments will be done at Days 43 (Week 6) and 85 (Week 12), the 'Since Last Visit CSSRS' will be completed. GSK Version 4.1 of both rating scales will be used.

Subjects who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their GP or appropriate psychiatric care and be discontinued from study medication. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 7.3.1 AE and SAE). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

7.4. Efficacy

7.4.1. Patient Reported Outcomes

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

7.4.1.1. Rheumatoid Arthritis Symptoms and Impact Diary

Symptoms associated with RA will be assessed using a novel RA Symptom and Impact Diary as per Section 7.1, Time and Events Table. The study staff should not clarify any of the questions for the subject.

7.4.1.2. Patient Assessment of Joint Pain

The severity of the subject's joint pain will be assessed by completion of a numeric rating scale (NRS). The subject will be asked to select a whole number (0-10 integers) that best reflects the intensity of their pain. The scale is represented by a horizontal bart with "no pain" at the lower anchor and "most severe pain" at the upper anchor. This questionnaire should take approximately 1 minute to complete.

The patient assessment of joint pain will be used to calculate ACR responders.

7.4.1.3. Patient's Global Assessment of Disease (PtGA)

Subjects will complete a global assessment of disease activity using the patient global assessment item, a visual analogue scale (VAS) with anchors "0" (very well) to "10" (very poor).

The patient's global assessment of disease will be used to calculate DAS clinical scores and ACR responders.

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

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.

This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas [Fries, 1980]:

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

Responses are scored from 0 (no difficulty) to 3 (inability to perform a task in that area).

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

7.4.1.5. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale

Subjects will complete a 13-point fatigue questionnaire using the FACIT-Fatigue assessment, a Likert scale from 0 to 4, to "0" (very much fatigued) to"4" (not at all fatigued). This questionnaire should take a few minutes to complete and provides the level of fatigue with usual daily activities from the previous week.

7.4.2. Clinical Disease Assessments

Brief details are given below and detailed procedural instructions are given in the SRM. The sponsor will calculate DAS28(CRP) and ACR (20/50/70) responses at each assessment time point as defined below.

7.4.2.1. Disease Activity Score (DAS) Assessments

The DAS28 is a measure of disease activity. It is a composite score derived measurement weighing given to each component.

The components of the DAS28 assessment include:

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

7.4.2.2. American College of Rheumatology Criteria (ACR) Assessments

The ACR Criteria is a standard criteria to measure the effectiveness of treatments from placebo. The ACR's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvement.

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

- Tender/Painful Joint count (28)
- Swollen Joint Count (28)
- Patient Assessment of Joint Pain
- PtGA
- PGA
- CRP
- HAQ-DI

7.4.2.3. Joint Assessments

Tender Joint Count Assessments
A total of 28 joints will be scored for presence or absence of tenderness.

Swollen Joint Count Assessments

A total of 28 joints will be scored for presence or absence of swelling.

Joint assessments will be used to calculate DAS28 clinical scores and ACR responders.

7.4.2.4. Measurement of Serum CRP

Blood samples will be collected in order to measure serum CRP concentrations. The CRP is a component of the DAS28, ACR, and Vectra DA clinical scores.

7.4.2.5. Physician's Global Assessment of Disease Activity (PGA)

The Investigator or physician designee only will complete a global assessment of disease activity using the physician global assessment item, a VAS with anchor's "0" (none) to "10" (extremely active).

Note:

- The Investigator or physician designee should complete the PGA independently of the subject.
- Ideally, the same Investigator or physician designee should perform all global assessments for each subject during the duration of the study.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for PK analysis of GSK2982772 will be collected at the time points indicated in Section 7.1 Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

For subjects who are on stable doses of methotrexate (MTX), blood samples for PK analysis of MTX will be collected at the time points indicated in Section 7.1 Time and Events Table. The actual date and time of each blood sample collection will be recorded.

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

7.5.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of GSK2982772

and MTX will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma sample has been analysed for GSK2982772 any remaining plasma sample may be analysed for other compound-related material and the results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.5.3. Synovial Biopsy Tissue for Pharmacokinetic Assay

See Section 7.6.2.2 for details on synovial tissue biopsy and procedure. If available, synovial tissue samples may be analysed for concentrations of GSK2982772 and possible drug-related material, as well as specific tissue distribution if feasible as sample availability allows.

7.5.4. Sample Analysis

Synovial biopsy sample analysis will be performed under the control of PTS IVIVT, GlaxoSmithKline. Information on processing the biopsies for the synovial pharmacokinetic assay will be provided in the laboratory manual. The results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.6. Biomarker(s)/Pharmacodynamic Markers

Pharmacodynamic biomarkers will be collected at the time points in Section 7.1 Time and Events Table and may include, but are not limited to, the following:

- Blood samples for mRNA expression e.g., IL6, MMP-1, MMP3, MMP-13, TIMP-1, MCP-1 and MIF.
- Blood samples for biomarkers which may be indicative of RA disease activity e.g., MRP8/14 and markers encompassed by Vectra DA.

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

7.6.1. Magnetic Resonance Imaging (MRI) of Joint

The most affected hand will be documented at baseline and used for all imaging visits. If subjects report both hands are equally involved, then the subject's dominant hand will be used.

DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability, only a standard MRI will be performed.

Each subject's most affected wrist (corresponding to the affected hand which is determined and documented at baseline) will be imaged by MRI at pre-dose on Days 1, 43 and 85 (see Section 7.1). If a scanning failure occurs at any visit, if feasible a rescan

is allowed within 7 days after the failed scan after consultation and agreement with the GSK Medical Monitor. There will be a minimum of 24 hours between scans where gadolinium (Gd) contrast is used. The MRI will be used in order to non-invasively quantify the degree of inflammation and structural changes within the target joint.

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

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

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

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

7.6.2. Synovial Biopsy

7.6.2.1. Selection of Joint for Synovial Biopsy

Synovial biopsies are optional for subjects enrolled in this study. There is no minimum number of subjects with joint biopsies required, but biopsies should be performed in as many subjects as possible. Synovial biopsy of a subject's swollen and tender wrist, knee or ankle joint will be performed at baseline (pre-dose Day 1). The final choice of joint is left to the discretion of the Investigator, although ideally it will be the most inflamed joint. The same joint should be biopsied at Day 43 (Week 6). If in the event that a repeat biopsy of the same joint as baseline is not possible, the joint may change if essential, after discussion with the GSK Medical Monitor. Any change must be documented in the CRF.

If a subject chooses to withdraw from the study after dosing and prior to Day 43, the Investigator must make every effort to perform a synovial biopsy if the subject has received at least 14 days of treatment with GSK2982772 or placebo.

7.6.2.2. Synovial Biopsy Procedure

Ultrasound imaging or arthroscopy will be used to guide the collection of approximately (as feasible for any given subject) of 6 synovial biopsies for immunohistochemistry (IHC), 6 synovial biopsies for pharmacokinetics, 6 synovial biopsies for target engagement, and 6 synovial biopsies for RNA extraction up to a combined maximum of 30 biopsies from the chosen joint under local anaesthesia (see SRM).

Biopsy tissue taken from synovial tissue will be divided accordingly for IHC, PK, target and pathway engagement, and gene expression. Histological assessment by IHC will be evaluated for general appearance and total inflammatory infiltrate. Specific cell numbers will also be analysed (which may include but are not limited to CD3+T-cells, CD55+ fibroblast-like synoviocytes, CD68+macrophages). mRNA may be isolated from synovial biopsys tissue, as feasibility dictates, to determine the effect of placebo and GSK2982772 on markers of inflammation and tissue healing (e.g., may include and not be limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1 and other chemokines and cytokines). Biopsy tissue collected for RNA transcriptional analysis may be utilised to determine the effect of GSK2982772 on cytokine and receptor expression, in addition to other markers of inflammation and tissue healing, as feasibility allows. For example, this may include but is not limited to, measurement of acute phase proteins, other chemokines and cytokines. Examples of technologies that may be used for these analysis include, but are not limited to, quantitative PCR, microarray, RNA sequencing or mass cytometry (CyTOF).

7.6.3. Novel Pharmacodynamic Biomarkers

7.6.3.1. RIP1 Target Engagement in Blood

Blood samples for RIP1 target engagement will be collected at the time points indicated in Section 7.1 to measure levels of free and drug-bound RIP1 protein.

7.6.3.2. RIP1 Target Engagement in Synovial Tissue

Synovial tissue biopsy samples will be collected at the time points indicted in Section 7.1 to measure levels of free and drug-bound RIP1 protein if sample quantity and data allow.

7.6.3.3. Pathway Biomarkers in Synovial Tissue

Synovial tissue biopsy samples will be collected at the time points indicated in Section 7.1 to measure total or phosphorylated RIP1, RIP3, MLKL and cleaved or total caspase 3 and caspase 8 if sample quantity and data allow.

7.6.4. Exploratory Novel Biomarkers

With the subject's consent, tissue and blood sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence disease/condition for study treatment, and/or medically related conditions, as well as the biological and clinical responses to GSK2982772. 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 GSK2982772 may be identified by application of:

- Gene expression analysis may be conducted on the blood and/or synovial biopsies using microarray, RNA sequencing and/or alternative equivalent technologies, which facilitates the simultaneous measurement (and confirmation) of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each synovial tissue sample.
- Soluble inflammatory mediators in the blood may be assayed for cytokine and inflammatory mediators including, but not limited to, pro-inflammatory and anti-inflammatory cytokines, chemokines, and acute phase proteins.

These analyses may be reported under separate protocol following the completion of the study. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

7.7. Genetics

In consenting subjects, a blood sample for pharmacogenetics (PGx) research will be drawn on Day 1 (or any time point post randomisation and prior to study completion) to better characterize genetic variability that may affect efficacy or safety endpoints. Information regarding pharmaogenetic (PGx) research is included in Appendix 4.

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 and date of birth will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of the study is to investigate the safety and tolerability of GSK2982772 following 12 weeks of treatment. No formal statistical hypotheses will be conducted to assess this objective.

If appropriate, comparisons between the GSK2982772 and the placebo arm will be made to investigate the secondary pharmacodynamic, mechanistic and efficacy objectives.

Trends over time will be investigated for both treatment arms along with associations between each of the pharmacodynamic, mechanistic and efficacy parameters.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

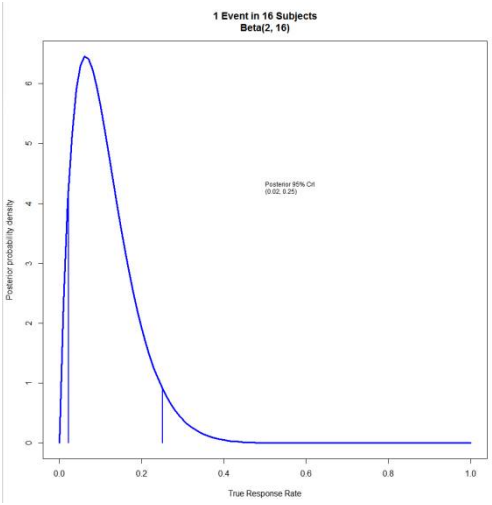
The study is not powered to detect pre-defined differences. A sufficient number of subjects will be screened so that approximately 24 subjects with moderate to severe RA are randomised into the study on a TID regimen. Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Table 4 summarises the total planned sample sizes for BID and TID regimens. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to an overall total maximum of 48) into the study at the discretion of the Sponsor.

Table 4 Summary of Total Sample Size by Dosing Regimen

Number Randomised to GSK2982772 60 mg BID or Placebo BID	Number Randomised to GSK2982772 60 mg TID or Placebo TID	Revised Max Total Sample Size	Total + Additional/ Replacement Subjects
7 - 12	24	36	42
12 - 18	24	42	48

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772 60 mg TID and up to 12 subjects randomised to GSK29827772 60 mg BID. Using a Bayesian approach to determine the confidence interval (CI) around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 16 then the posterior distribution would be Beta (2, 16), as outlined below in Figure 4.

Figure 4 One Event in 16 Subjects: Beta (2,16) Distribution



Thus, we can be 95% certain that the true probability of the safety event lies between 2% and 25%.

For supportive information, the properties of the key secondary endpoint DAS28 have been considered.

Based on the estimate of variability (SD=1 from historical data) it is estimated that the lower and upper bounds of the 95% CI for the change from baseline in DAS28-CRP score will be within approximately 0.693 and 0.490 of the point estimate of GSK2982772 60 mg TID (n=16) and placebo (n=8).

9.2.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is higher or lower than 16 in the GSK2982772 group, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in Table 5.

Table 5 Sample Size Sensitivity

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
20	0	16.1%
20	1	23.8%
20	2	30.4%
18	0	17.6%
18	1	26.0%
18	2	33.1%
16	0	19.5%

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
16	1	28.7%
16	2	36.4%
14	0	21.8%
14	1	31.9%
14	2	40.5%
12	0	24.7%
12	1	36.0%
12	2	45.4%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be conducted.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All Subjects Population: The 'All Subjects Population' is defined as subjects who were screened for the study. This population is used for the summary of selected accountability data.

Safety Population: The 'Safety Population' is defined as subjects who receive at least one dose of study medication. This population is used for the summary of all data including demography, safety, efficacy and exploratory data but excluding PK data.

Pharmacokinetic Population: The 'PK Population' is defined as subjects in the 'Safety' population who received an active dose and for whom a GSK2982772 pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only. Any PK-PD analysis will be conducted on the Safety population such that subjects receiving placebo can be included.

If 12 or more subjects are randomised to a BID regimen (i.e., ≥4 placebo and ≥8 GSK2982772 60 mg BID) then treatment received will take into account dosing frequency for GSK2982772, otherwise treatment will be irrespective of dosing frequency.

9.3.2. Interim Analysis

A formal interim analysis will be conducted during the study. Additionally, two review teams will monitor data on an ongoing basis for routine pharmacovigilance and decision making regarding the subsequent clinical development of GSK2982772 for RA.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT) which will include members of the GSK2982772 project team, will review blinded safety

data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK Project Physician Lead (PPL), the study statistician, the study pharmacokineticist, the PRR DPU Head, EDL and SRT Leader or designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data. The primary purpose of these informal reviews will be to monitor DAS28-CRP for futility. On review of DAS28-CRP data, the review group may recommend an interim analysis of key clinical and mechanistic data is first conducted prior to any decision to terminate the study for futility. A data review charter will identify the specific GSK individuals involved, outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted during the study. The timing of this analysis will either be on the recommendation of the data review group to assess futility based on 6 weeks of treatment, or when an appropriate number have completed 12 weeks of treatment, whichever is earliest. The purpose of the Interim Analysis would be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

All safety evaluations will be based on the Safety population. Clinical interpretation will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead ECG monitoring.

9.4.2. Secondary Analyses

The relationship between each of the mechanistic endpoints and also with the clinical endpoints will be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g., DAS28-CRP score). This may be conducted through comparing statistical models incorporating different explanatory terms (i.e. mechanistic endpoints) with the ‘null’ model (no mechanistic endpoints); or if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed.

Each endpoint will be considered individually and at the treatment level, where comparisons between treatment groups would be made on any changes observed, if deemed appropriate. This could include change from baseline in DAS28-CRP, which will be statistically analysed using a MMRM analysis comparing GSK2982772 with placebo

at each time point. Additionally, this could include, the proportion of subjects achieving ACR20/50/70 and DAS28-CRP response, which will be statistically analysed using a Generalised Estimating Equation (GEE) model comparing GSK2982772 with placebo at each timepoint. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

9.4.3. Other Analyses

In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain change in DAS28 (i.e., comparator rate), based on the data that we have observed in the study.

GSK2982772 plasma concentrations will be summarised descriptively by day and nominal sampling time.

Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

9.4.3.1. Exploratory Analyses

All exploratory endpoints will be descriptively summarised, graphically presented and listed appropriately. Further details can be found 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

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) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the Investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

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

10.6. Records Retention

- Following closure of the study, the Investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The Investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator is no longer associated with the site.

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

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

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

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

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMD	Age-related macular degeneration
Anti-CCP	Anti-Cyclic Citrullinated Peptide
Anti-dsDNA	Anti-double stranded deoxyribose nucleic acid
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BID	Twice a day
CARLOS	Cartilage Loss Scoring System
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-Reactive Protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CYP	Cytochrome P
DAS	Disease Activity Score
DAS28	Disease activity score for 28 different joints
DAS28(CRP)	Disease activity score for 28 different joints with CRP value
DCE	Dynamic contrast enhanced
DNA	Deoxyribose Nucleic Acid
DMARD	Disease-Modifying Antirheumatic Drugs
DPU	Discovery Performance Unit
DRC	Data Review Committee
ECG	Electrocardiogram
EDL	Early Development Lead
EMA	European Medicines Agency
ETCO2	End-tidal Carbon Dioxide
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTiH	First Time in Human
GCP	Good Clinical Practice

Gd	Gadolinium
GEE	Generalised Estimating Equations
GFR	Glomerular Filtrate Rate
GSK	GlaxoSmithKline
HAQ-DI	Disability Index of the Healthy Assessment Questionnaire
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
IRE	Initial rate of enhancement
IRTS	Interactive Response Technology System
Kg	Kilogram
L	Litre
LDL	Low Density Lipoprotein
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxy-methamphetamine
ME	Maximal signal intensity enhancement
MedDRA	Medical Dictionary for Regulatory Activity
mg	Milligram
mL	Millilitre
MLKL	Mixed lineage kinase domain-like protein
mm	Millimeter
mmol	Millimole
MMP	Matrix metallopproteinase
MMRM	Mixed-effect Model Repeat Measurements
MRI	Magnetic Resonance Imaging
msec	millisecond
MRP	Myeloid-related Protein
MSDS	Material Safety Data Sheet
MTX	Methotrexate
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NOAEL	No Adverse Effect Level
NONMEM	Non Linear Mixed Effect Model
NRS	Numeric Rating Scale

NSAID	Non-steroidal anti-inflammatory drug
NSF	Nephrogenic Systemic Fibrosis
OMERACT	Outcome Measures in Rheumatology
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PGA	Physician's Global Assessment of Disease
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetic
PPD	Tuberculin Purified Protein Derivative
PPL	Project Physician Lead
PRO	Patient Reported Outcome
PRR	Pattern Recognition Receptor
PSRAE	Possible Suicidality Related Adverse Event
PtGA	Patient Global Assessment of Disease
PTS IVIVT	Platform Technology and Science In Vitro/In Vitro Translation
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
R&D	Research and Development
RAP	Reporting and Analysis Plan
RAMRIQ	Rheumatoid arthritis MRI quantitative
RAMRIS	Rheumatoid arthritis MRI scoring system
RBC	Red Blood Cell
RF	Rheumatoid factor
RIP1	Receptor-interacting protein-1
RIP3	Receptor-interacting protein-3
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SIB	Suicidal Ideation Behaviour
SLE	Systemic lupus erythematosus
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SpO2	Peripheral Capillary Oxygen Saturation
SRM	Study Reference Manual
SRT	Safety Review Team
TB	Tuberculosis
TEAR	Target Engagement Assay RIP1
TID	Three times a day
TIMP	Tissue inhibitor of metalloproteinases

TLR	Toll-like receptor
TNF	Tumor necrosis factor
TTS	Technical Terms of Supply
UK	United Kingdom
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
WOCP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
QuantiFERON
Sugita
Vectra DA

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>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, stabilize, or return to within baseline (see MONITORING below)
Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study</td><td>Viral hepatitis serology[4]
Blood sample for pharmacokinetic (PK) analysis, obtained within 2 days after last dose[5]
Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
Fractionate bilirubin, if total bilirubin≥2xULN
Obtain complete blood count with differential to assess eosinophilia
Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
Record use of concomitant medications</td></tr>
</table>

treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 **hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24**-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<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]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

12.3. Appendix 3: Prednisolone Equivalent Dose Table

Drug Name	**Dose Equivalent to 1 mg Oral Prednisone**
Cortisone acetate	5 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg
Dexamethasone	0.15 mg

12.4. Appendix 4- 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 GSK2982772 or any concomitant medicines;
- Rheumatoid arthritis susceptibility, severity, and progression and related conditions

GSK2982772 is a novel first-in-class asset being introduced to patients with moderate to severe RA for the first time. Currently its mechanism of action is not fully characterised nor understood.

Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance. In addition, continuing research may identify other enzymes, transporters, proteins ore receptors that may be involved in response to GSK2982772. The genes that may code for these proteins may also be studied. Genome-wide scans involving a large number of polymorphic markers (e.g. single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene does not exist and/or the potential genetic effects are not well understood.

Genetic data may be generated while the study is underway or following completion of the study. Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

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

Study Population

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

Study Assessments and Procedures

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

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

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

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK2982772 has been completed and the study data reviewed. In some cases, the samples may not be studied.

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 and Baseline Failures

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

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

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic

studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

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

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

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.5.2. Definition of Serious Adverse Events

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

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

Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Is associated with liver injury and 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

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

12.5.4. 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 PRO questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the PRO 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.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

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

12.5.6. 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 Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The Investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.6.1. 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 sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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

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 90 days after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
   - Contraceptive subdermal implant
   - Intrauterine device or intrauterine system

- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]

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

12.6.2. 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 fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to GSK as described in Appendix 4 While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will discontinue study medication or 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 and up to 90 days after the last dose of study medication. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.

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

12.7. Appendix 7: - Country Specific Requirements

Protocol Amendment 04 (03-AUG-2017) is a country specific amendment for Germany which reinstates specific clinical laboratory criteria in Exclusion Criteria 23 and Haematologic Stopping Criteria in Section 5.4.5 that was changed in Amendment 03 (20-APR-2017).

The following applies to subjects recruited and enrolled in Germany:

Section 5.2 Exclusion Criteria

Diagnostic assessments and other criteria

23. Haemoglobin <11 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L); platelet count ≤100,000/μL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at screening.

Section 5.4.5 Haematologic Stopping Rules

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 ≥2 g/dL from baseline (pre-dose Day 1).
- Platelets <50 × 10^9/L

12.8. Appendix 8: Protocol Amendment Changes

12.8.1. Amendment 4 (03-AUG-2017) from Protocol Amendment 3 (20-APR-2017)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in Germany only.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 04 is a country specific amendment for Germany which reinstates the clinical laboratory criteria in Exclusion 23 and Haematologic Stopping Criteria in Section 5.4.5 that was changed in Amendment 03.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Section 5.2 Exclusion Criteria

Diagnostic assessments and other criteria

23. Haemoglobin <9 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L); platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at screening. ***For subjects recruited in Germany: Haemoglobin <11 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L); platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at screening.***

Section 5.4.5 Haematologic Stopping Rules

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

- Haemoglobin - an absolute decrease of ≥2 g/dL from baseline (pre-dose Day 1). ***For subjects enrolled in Germany: Haemoglobin <9 g/dL (5.58 mmol/L) or an absolute decrease of ≥2 g/dL from baseline (pre-dose Day 1).***
- Platelets <50 × 10^9/L

12.8.2. Amendment 3 (20-APR-2017) from Protocol Amendment 2 (14-JUL-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 03 incorporates change in dosing regimen from 60 mg BID to 60 mg TID, restrictions on JAK inhibitors, defined non-reproductive potential criteria in Exclusion 11, change to clinical laboratory criteria in Exclusion 23, of evaluation of joint space narrowing with MRI, flexibility in scheduling with MRI and synovial biopsy.

GlaxoSmithKline Document Number of Investigator Brochure GSK2982772 has been updated to 2014N204126_02 throughout the document. Other minor protocol clarifications and administrative changes are also provided in this amendment.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Authors

Author (s): PPD

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	**Tel** PPD **Email** PPD ~~Mobile:~~ PPD ~~Email:~~ PPD	**Mobile** PPD PPD PPD ~~Mobile:~~ PP PPD	**N/A** PPD	**GSK Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, UK** ~~UP4440~~ ~~1250 S~~ ~~Collegeville, PA 19426 USA~~
Secondary Medical Monitor		**Mobile:** PPD **Email** PPD ~~Tel:~~ PPD ~~Mobile:~~ PPD ~~Email:~~ PPD	**Mobile** PPD PPD ~~Mobile:~~ PPD	**NA** PPD PPD	**1250 S. Collegeville Rd. Collegeville PA 19426, USA** ~~Cytokine Chemokine DPU, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, UK~~
SAE contact information	Medical Monitor as above				

Synopsis and Section 2.1 Study Rationale

The primary objective of this study has not changed with amendment 03; however the dosing regimen does change to GSK2982772 (60 mg three times daily for 84 days).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg ~~twice~~ **three times daily** for 84 days). In addition to the pharmacokinetics (PK), a number of experimental and clinical endpoints will be employed to obtain information on the pharmacodynamics (PD), and preliminary efficacy in subjects with active RA. Although no formal hypothesis will be tested, these endpoints will enable a broader understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in RA, by making full use of the information obtained from each subject enrolled.

Synopsis and Section 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg ~~twice~~ **three times** daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8 and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 **mg** ~~twice~~ **three times** daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Magnetic Resonance Imaging (MRI) parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, ~~and~~ bone oedema **and joint space narrowing** as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, **the** RAMRIQ (Rheumatoid arthritis MRI quantitative) scoring system, **the modified CARLOS (Cartilage Loss Scoring System)** and additional exploratory endpoints as data permit. • Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:

Objectives	Endpoints
	• Exchange rate (K^{trans}) • Interstitial volume (V_e) • Plasma volume (V_p) • Initial rate of enhancement (IRE) • Maximal signal intensity enhancement (ME) • Joint volume • Enhancing volume
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg ~~twice~~ **three times** daily dosing of GSK2982772 on methotrexate (MTX) concentrations.	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue from subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.

• To investigate pathway and target engagement following 60 mg ~~twice~~ **three times** daily doses of GSK2982772 in blood and synovial biopsy tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit:
	  • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue.
	  • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.

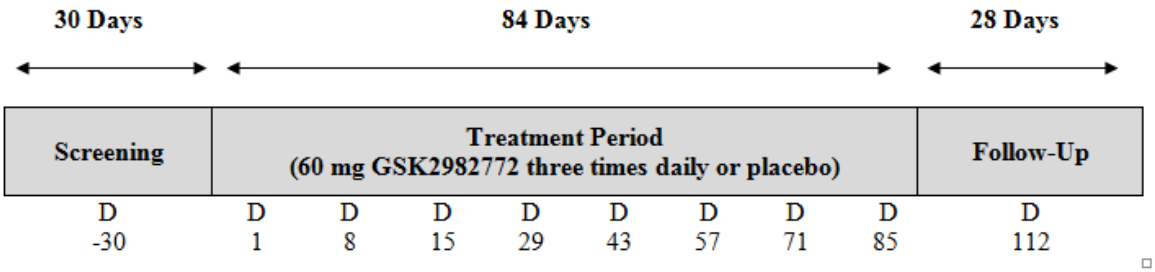
• To investigate the concentration of	• Pre-dose GSK2982772 synovial tissue

Objectives	Endpoints
GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg ~~twice~~ **three times** daily doses of GSK2982772.	biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit.
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on gene expression in the blood subjects with active moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg ~~twice~~ **three times** daily doses of GSK2982772 on gene expression in the synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

Synopsis and Section 4.1 Overall Design

Schematic added.

Amendment 03:



Synopsis Treatment Arms and Duration

Subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg ~~twice~~ **three times** daily (~~BID~~ **TID**)

Placebo **three times** daily (~~BID~~ **TID**)

Prior to amendment 03 being effective in each country, subjects have been randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg two times daily (BID)

Placebo two times daily (BID)

Synopsis and Section 4.3 Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately ~~30~~ **24** subjects with moderate to severe RA are randomised into the study **on a TID regimen. Prior to protocol amendment 03 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen**. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to ~~a~~ **an overall total** maximum of ~~36~~ **48**) into the study at the discretion of the Sponsor.

Section 4.2.2 Treatment Period

Subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally ~~twice~~ **three times** daily (approximately ~~12~~ **8** hours apart) for 84 days (12 weeks**). Subjects that were randomised prior to protocol amendment 03 being approved in each country were randomly assigned to either GSK2982772 60 mg or placebo orally two times daily (approximately 12 hours apart) for 84 days (12 weeks).**

During the 84 day (12 week) treatment period, subjects will attend the clinical site for visits on Days 1, 8, 15, 29, 43, 57, 71 and 85. At specific visits, subjects must not take study treatment prior to their scheduled visit (see Section 7.1). On Days 22, 36, 50, 64 and 78, each subject will be contacted by telephone and asked about their general health**, study medication compliance and diary card completion. Subjects will be given a diary card at each of the visits on which they will be instructed** to record their daily study medication and concomitant medication taken and any adverse events.

Section 4.3 Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately ~~30~~ **24** subjects with moderate to severe RA are randomised into the study **on a TID regimen**. **Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen.** Should the **overall** drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to ~~a~~ **an overall total** maximum of ~~36~~ **48**) into the study at the discretion of the Sponsor.

Section 4.4 Design Justification

The subjects will be randomised in a 2:1 ratio to GSK2982772 60 mg ~~twice daily (BID)~~ **three times daily (TID)** and placebo respectively. The primary objective of this study is

to assess safety and tolerability, and assessment of this is most valuable in a placebo controlled study. The placebo group was also deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication and dose is stable throughout the study.

Section 4.5 Dose Justification

The **initial** selection of the 60 mg BID dose ~~to be~~ **being** tested in this study is based on the safety, PK, and PD data from the First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was **initially** selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2h). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose **was**~~is~~ predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects will have >90% target engagement in blood at C_{min} **using a novel in-house ex-vivo PD/target engagement assay based solely on the TNF pathway which is believed to be a key component of the RIP1 pathway**.

However, based on final PK/PD modelling from the full repeat dose part of the Study 200975 (up to 120 mg BID), a 60 mg BID dose is now predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >85% target engagement at C_{min}. This is lower than our target of achieving >90% target engagement in at least 90% of subjects at C_{min}. Therefore, a 60 mg TID cohort is now being proposed.

The C_{min} values at 60 mg TID are predicted to be approximately 3.5 fold higher than for 60 mg BID. Using the final PK/PD, a 60 mg TID dose is predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have > 96% target engagement at C_{min}. No data are currently available about the distribution of GSK2892772 into the synovium. Based on data in non-steroidal anti-inflammatory drugs (NSAIDs), the synovial fluid concentrations fluctuate to a much lesser extent than those in plasma [Netter, 1989]. Peak drug concentrations are generally lower in synovial fluid but are similar to plasma at later time points. Assuming the same is true for GSK2982772, a 60 mg ~~BID~~**TID** dose should provide similar RIP1 target engagement at the site of action as predicted in blood.

In addition, because of the short half-life, a modified release formulation is now being developed with the aim to provide a once daily dosing regimen. By increasing the frequency of dosing to three times daily (TID) with the current immediate release formulation, this will more closely match the PK, safety and efficacy profile of a preferred once daily modified release formulation.

The safety of increasing the dose frequency to 60 mg TID is justified based on nonclinical safety findings to date with GSK2982772. It is anticipated that a human dose of 60 mg TID (180 mg/day) will produce $AUC_{(0-24)}$ and C_{max} values of approximately 9.9 ug.h/mL and 0.8 ug/mL, respectively, which are approximately

1/5th and 1/15th of the gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

As of 03 Apr 2017, a total of approximately 93 subjects across 4 clinical studies have been randomised to receive GSK2982772. In Study 200975, GSK2982772 administered up to 120 mg BID for 14 days and was well tolerated and no safety concerns were identified. A total of 9 subjects had received 120 mg BID in that study. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. In the ongoing Phase 2a studies in Psoriasis [(PsO); Study 203167] and Rheumatoid Arthritis [(RA); Study 203168], a total of 26 subjects have been randomised to GSK2982772 60 mg BID. GSK2982772 was well tolerated and no drug-related SAEs have been reported. In Study 203167, there was a death of a 19 year old male subject due to an accidental overdose with 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

~~Therefore, it is predicted that a dose of GSK2982772 60 mg BID may be clinically efficacious in subjects with RA.~~

~~It is anticipated that a human dose of 60 mg BID will produce area under the concentration-time curve ($AUC_{[0-24]}$) and maximum observed concentration (C_{max}) values of approximately 9 µg.h/mL and 1 µg/mL, respectively, which are approximately 1/6th and 1/12th of the gender-averaged AUC (48.4 µg.h/mL) and C_{max} (12.3 µg/mL) achieved in the 13-week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day.~~

Section 5.1 Inclusion Criteria

Sex

11. Male & Female subjects

Females:

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

a. Non-reproductive potential ~~as~~ defined **as** ~~in Appendix 6~~:

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

- **Documented Bilateral Oophorectomy**

- **Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods (see Appendix 6) 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.**

Section 5.2 Exclusion Criteria

Diagnostic assessments and other criteria

23. Haemoglobin <~~11~~**9** g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L) ~~or ≥14,000/mm^3 (≥14 x 10^9/L)~~; platelet count ≤100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤~~3~~**1.5** x 10^9/L~~; lymphocyte count <1 x 10^9/L~~ at screening.

Section 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 Case Report Form (CRF).
- The Sponsor's request, for reasons such as significant protocol deviations **or subject safety concern** (and after discussion with the Investigator).
- If a subject is withdrawn from study treatment, this subject is also considered to be withdrawn from the study.
- Study is terminated by the Sponsor.

Section 5.4.5 Haematologic Stopping Rules

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~~**2** g/dL from baseline (pre-dose Day 1)
- ~~Neutrophils <1 × 10^9/L~~

- ~~Lymphocytes <0.5 × 10^9/L~~
- Platelets <50 × 10^9/L

Section 6.1 Investigation Product and Other Study Treatment

	Study ~~Treamtent~~ Treatment	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions (with amendment 03):	**Take TWO tablets three times a day as directed by your physician**	**Take TWO tablets three times a day as directed by your physician**
Dosing instructions **(prior to amendment 03):**	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Physical description:	White to almost white, round, film coated tablet	White to almost white, round, film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

Section 6.4 Blinding

Sponsor unblinded refers only to the Data Review Committee (DRC) consisting of the GSK ~~study physician~~ **Project Physician Lead (PPL),** the study statistician, the study pharmacokineticist, Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head, the Early Development Leader (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis.

Section 6.7 Compliance With Study Treatment Administration

Subjects will be given instructions on compliance and treatment with MTX (if applicable). The date, time and total weekly dose will be recorded in **the study diary cards and** the CRF.

Section 6.8 Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 >~~120~~**180** mg daily will be considered an overdose. GSK does not recommend specific treatment for an overdose. The Investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

Section 6.11.1 Permitted Medications and Non-Drug Therapies

Table 1

Drug	Requirement
Methotrexate	Stable dose regimen (up to 25 mg/week) for at least 12 weeks prior to screening and remain on this dose throughout the study (unless dose must be reduced because of a safety concern). MTX should **ideally** be taken on the same day of week and at approximately the same time of day throughout the study.

Section 6.11.2 Prohibited Medications and Non-Drug Therapies

Table 2

Therapy	**Time period**
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
Janus Kinase (JAK) Inhibitors	**4 weeks prior to screening until after the follow up visit (Day 112).**
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112).
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	4 weeks prior to the first dose (Day 1) until after the follow up visit (Day 112).
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time.

Therapy	Time period
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 ~~½~~ **half** lives (whichever is longer) prior to first dose until after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

Section 7.1 Time and Events Table

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------															----------X
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4, 20]						X[4,~~20~~21]						X[22]	X[16]	

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
Study Treatment																
Randomisation		X														
Study medication (~~twice~~**three times** daily)[8]		X----------												X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4,**20**]						X[4,~~19~~**21**]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).

2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact. On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.
6. All PRO assessments should be conducted **on site** before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).
8. Subjects must take study medication ~~twice~~**three times** a day approximately ~~12~~ 8 hours apart. Exact time of dosing to be recorded in diary cards. On Day 1, the first study dose will be administered at the site. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71. **When clinical laboratory samples are taken on the same day as the MRI, the samples should be taken first prior to the administration of the contrast fluid with MRI. If this is not feasible (i.e. MRI is performed first), it is recommended that a separate IV catheter or straight venipuncture be performed in the *opposite* arm to where the MRI contrast fluid was administered.**
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours. **A**~~and~~ **trough PK sample will be taken** on Day 85 or at Early Withdrawal.
13. **Only applicable if subjects are on MTX:** PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX ~~must~~ should ideally take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits ~~must~~should ideally be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit. **A window allowance of ± 3 days of Early Withdrawal visit is allowed to perform the MRI**.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.
20. **MRI (and if applicable; a biopsy) may be performed during the screening window as an additional visit (if required) up to 7 days before Day 1 to allow sites flexibility in scheduling. The MRI must be completed prior to synovial biopsy (if performed on the same joint). The site should be reasonably confident that the subject has fully qualified for the study (e.g., screening clinical labs, vital signs, physical examination, etc.) before the MRI (and if applicable: a biopsy) is/are performed.**

21. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (±3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.
22. **For MRI performed on day 85, a visit window of up to 2 days after is allowed in order to perform the MRI.**

Section 7.3.5 Electrocardiogram (ECG)

- Triplicate12-lead ECGs will be obtained at screening and single 12-lead ECGs obtained at every time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F or B) intervals. **A manual over read is also allowed.** Refer to Section 5.4.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.

Section 7.3.7 Suicidal Risk Monitoring

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. **Study medication must be immediately discontinued in a**ll subjects who experience signs of suicidal ideation or behaviour ~~must immediately be discontinued from study medication~~.

Section 7.6.1 Magnetic Resonance Imaging (MRI) of Joint

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

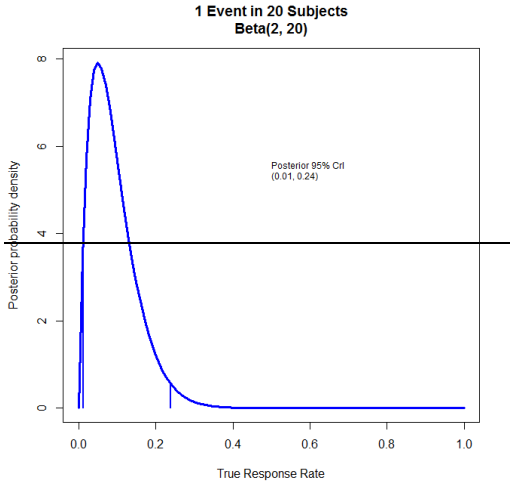
Section 9.2.1 Sample Size Assumptions

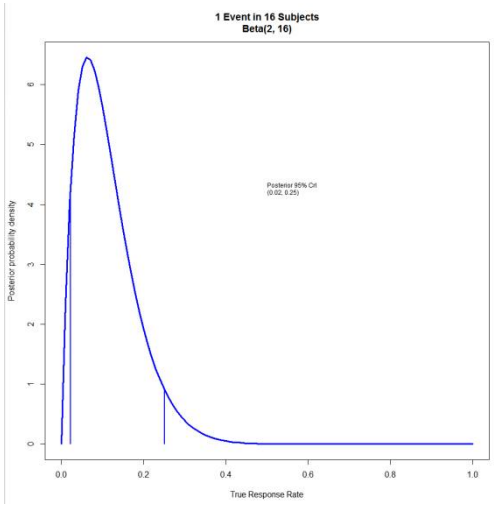
The study is not powered to detect pre-defined differences. A sufficient number of subjects will be screened so that approximately **24**~~30~~ subjects with moderate to severe RA are randomised into the study **on a TID regimen. Prior to protocol amendment 3 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Table 4 summarises the total planned sample sizes for BID and TID regimens.** Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to **an overall** maximum of **48**~~36~~) into the study at the discretion of the Sponsor.

Table 4 Summary of Total Sample Size by Dosing Regimen

Number Randomised to GSK2982772 60 mg BID or Placebo BID	Number Randomised to GSK2982772 60 mg TID or Placebo TID	Revised Max Total Sample Size	Total + Additional/ Replacement Subjects
7 - 12	24	36	42
12 - 18	24	42	48

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772 **60 mg TID and up to 12 subjects randomised to GSK29827772 60 mg BID.** Using a Bayesian approach to determine the confidence interval (CI) around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in ~~20~~ **16** then the posterior distribution would be Beta (2, ~~20~~**16**), as outlined below in Figure 4.





Thus, we can be 95% certain that the true probability of the safety event lies between ~~0.01~~**2%** and ~~0.24~~**25%**.

For supportive information, the properties of the key secondary endpoint DAS28 have been considered.

Based on the estimate of variability (SD=1 from historical data) it is estimated that the lower and upper bounds of the 95% CI for the change from baseline in DAS28-CRP score will be within approximately ~~0.694~~**0.693** and ~~0.462~~**0.490** of the point estimate of GSK2982772 **60 mg TID** (n=~~20~~**18**) and placebo (n=~~10~~**8**).

Section 9.2.2 Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is **higher or** lower than **16** in the GSK2982772 group, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in **Table 5.**

Table 5 Sample Size Sensitivity

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
20	0	16.1%
20	1	23.8%
20	2	30.4%
18	0	17.6%
18	1	26.0%
18	2	33.1%
16	0	19.5%
16	1	28.7%
16	2	36.4%
14	**0**	**21.8%**
14	**1**	**31.9%**
14	**2**	**40.5%**
12	**0**	**24.7%**
12	**1**	**36.0%**
12	**2**	**45.4%**

Section 9.3.1 Analysis Populations

If 12 or more subjects are randomised to a BID regimen (i.e., ≥4 placebo and ≥8 GSK2982772 60 mg BID) then treatment received will take into account dosing frequency for GSK2982772, otherwise treatment will be irrespective of dosing frequency.

Section 9.3.2 Interim Analysis

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK ~~study physician~~**Project Physician Lead (PPL)**, the study statistician, the study pharmacokineticist, the PRR DPU Head, EDL and SRT Leader or designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data.

Section 11.0 References

GlaxoSmithKline Document Number 2014N204126_**02**. Investigator Brochure for GSK2982772. Report Date **27-JAN-2017**.

Section 12.1. Appendix 1 – Abbreviations and Trademarks

Anti-CCP	**Anti-Cyclic Citrullinated Peptide**
CARLOS	**Cartilage Loss Scoring System**
hCG	**Human Chorionic Gonadotropin**
LDL	**Low Density Lipoprotein**
MCV	**Mean Corpuscular Volume**
MDMA	**3,4-methylenedioxy-methamphetamine**
PPL	**Project Physician Lead**
SGOT	**Serum Glutamic Oxaloacetic Transaminase**
SGPT	**Serum Glutamic Pyruvic Transaminase**
TID	**Three times daily**
WOCP	**Women of Child Bearing Potential**

Section 12.4 Appendix 4 – Genetic Research

Genetic Research Objectives and Analyses

GSK2982772 is a novel first-in-class asset being introduced to patients with moderate to severe RA for the first time. Currently its mechanism of action is not fully characterised nor understood.

Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance. In addition, continuing research may identify other enzymes, transporters, proteins ore receptors that may be involved in response to GSK2982772. The genes that may code for these proteins may also be studied. Genome-wide scans involving a large number of polymorphic markers (e.g. single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene does not exist and/or the potential genetic effects are not well understood.

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

If applicable and genetic research is conducted, ~~A~~appropriate descriptive and/or statistical analysis methods will be used **to evaluate pharmacogenetic data in the context of the other clinical data**. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

12.8.3. Amendment 2 (14-JUL-2016) from Protocol Amendment 1 (25-MAY-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 02 incorporates addition of suicidal ideation and behaviour (SIB) withdrawal criteria.

Other minor protocol clarifications and administrative changes are also provided in this amendment.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Authors

Author (s): PPD

Author (s): PPD

MEDICAL MONITOR/SPONSOR INFORMATION

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	~~Tel:~~ PPD Mobile: PPD PPD Email: PPD PPD	Mobile: PP PPD PPD PPD	PPD	~~Pattern Recognition Receptor DPU,~~ UP4440 1250 S Collegeville, PA 19426 USA
Secondary Medical Monitor		Tel: PPD Mobile: PPD Email: PPD	Mobile: PPD PPD		Cytokine Chemokine DPU, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, UK
SAE contact information	Medical Monitor as above				

Section 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 medications for the treatment of RA as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or Haematologic stopping criteria (Section 5.4.5) are met.
- **The subject experiences any signs of suicidal ideation or behaviour (Section 7.3.7).**

Section 7.1 Time and Events Table

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact. **On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.**
6. All PRO assessments should be conducted before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. **If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).**
8. Subjects must take study medication twice a day approximately 12 hours apart. Exact time of dosing to be recorded in diary cards. **On Day 1, the first study dose will be administered at the site.** On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or at Early Withdrawal.
13. PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX must take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits must be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.
20. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (±3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.

Section 7.2 Screening and Critical Baseline Assessments

Medical/medication/**mental health and** family history, ECG and laboratory tests will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Section 7.3.7 Suicidal Risk Monitoring

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. ~~Consideration should be given to discontinuing GSK2982772 in s~~**All s**ubjects who experience signs of suicidal ideation or behaviour **must immediately be discontinued from study medication**.

Families and caregivers of subjects being treated with GSK2982772 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study Investigator.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening CSSRS' will be completed. **Assessments will be done at** ~~At~~ Days 43 (Week 6) and 85 (Week 12), the 'Since Last Visit CSSRS' will be completed. GSK Version 4.1 of both rating scales will be used.

Subjects who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their GP or appropriate psychiatric care **and be discontinued from study medication**. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 7.3.1 AE and SAE). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

12.8.4. Protocol Amendment 1 (25-MAY-2016) from the original protocol (01-APR-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

Summary of Protocol Amendment Changes with Rationale

Protocol Amendment 01 incorporates the addition of risk text for drug interaction with P-glycoprotein (Pgp) inhibitors and narrow therapeutic index (NTI) CYP3A4 substrates, and an updated list of prohibited medications.

Other minor protocol clarifications and administrative changes are also provided in this amendment.

List of Specific Changes (bold indicates text added and ~~strikethrough~~ indicates text removed**):**

Section 1 Protocol synopsis, Analysis, Paragraph 2

An ongoing review of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GlaxoSmithKline (GSK) individuals, some of whom are also members of the GSK study team **who are not involved in the day-to-day running of the study.**

Section 4.5 Dose Justification

It is anticipated that a human dose of 60 mg **BID** will produce area under the concentration-time curve ($AUC_{[0-24]}$) and maximum observed concentration (C_{max}) values of approximately 9 μg.h/mL and 1 μg/mL, respectively, which are approximately $1/6^{th}$ and $1/12^{th}$ of the gender-averaged AUC (48.4 μg.h/mL) and C_{max} (12.3 μg/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day.

Section 4.6.1 Risk Assessment

Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing ~~uptake of~~ **potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and** OAT3 **substrates** were completed. **To date, formal drug interaction studies in humans have not been performed with GSK2982772.** There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. MTX is an OAT3	**Subject Selections**: • **Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. See Section 6.11.2 for a comprehensive list of medications.** **Subject Monitoring:** • **Subjects' concomitant medication usage will be**

	substrate in which GSK2982772 could potentially impair the clearance of MTX. **There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772.** **GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772.** **See Section 4.3.6 of the GSK2982772 IB [GlaxoSmithKline Document 2014204126_01].**	**reviewed prior to inclusion and monitored throughout the study.** • **Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.** • PK sample collection to evaluate the potential interaction of GSK2982772 and MTX will be performed throughout the study. • Subjects should be monitored for potential effects of interaction between GSK2982772 and MTX. • Clinical laboratory results (e.g., liver function tests) are routinely being monitored throughout the study.

Section 5.2 Exclusion Criteria, Contraindications

CONTRAINDICATIONS
19. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
20. Received a live or attenuated vaccine within 30 days of randomization OR plan to receive a vaccination during the study until **5** half-lives (or 2 days) plus 30 days after receiving GSK2982772.
21. Contraindication to gadolinium contrast agent in accordance with local guidelines.
22. The subject has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer before the first dose of study medication, or plans to take part in another clinical trial at the same time as participating in this clinical trial.

Section 6.4 Blinding

This will be a double blind (sponsor unblinded) study and the following will apply:

- Sponsor unblinded refers only to the Data Review Committee, consisting of the GSK study physician, study statistician, study pharmacokineticist, **Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head,** Early Development Lead (EDL) and Safety Review Team (SRT) Leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this

review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.

Section 6.11.2 Amended Prohibited Medications and Non-Drug Therapies, Table 2 Prohibited Medications

Therapy	**Time period**
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	**4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112).**
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	**4 weeks prior to the first dose (Day1) until after the follow up visit (Day 112).**
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time.
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 ½ lives (whichever is longer) prior to first dose until

Therapy	Time period
	after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

Section 7.1 Time and Events Table

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------															----------X
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4]						X[4,20]						X	X[16]	

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Study Treatment																
Randomisation		X														
Study medication (twice daily)[8]		X----------												----------X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, ~~Anti-CARP,~~ RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4]						X[4,20]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact.
6. All PRO assessments should be conducted before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist.
8. Subjects must take study medication twice a day approximately 12 hours apart. Exact time of dosing to be recorded in diary cards. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or at Early Withdrawal.
13. PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX must take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits must be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.
20. **A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance (± 3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.**

Section 7.2 Screening and Critical Baseline Assessments

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

Section 7.3.4 Vital Signs

Vital signs will be measured in **a supine or** semi-supine position after approximately 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

Section 7.3.6 Clinical Safety Laboratory Assessments, Table 3 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology [1,2]</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [3]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose[4]</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>CRP</td><td>Triglycerides[4]</td><td>Total Cholesterol[4]</td><td>Fasting HDL cholesterol[4]</td></tr>
<tr><td>Fasting LDL cholesterol[4]</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravitypH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening and RoutineTests</td><td>• HIV 1 & 2
• Hepatitis B (HBsAg)
• Hepatitis B core antibody (HBcAb)
• Hepatitis C (Hep C antibody)
• QuantiFeron Gold Test
• T-spot (if QuantiFeron is indeterminant)
• FSH and estradiol (as needed in women of non-child bearing potential only)
• Urine hCG Pregnancy test (as needed for women of child bearing potential) [5]
• Serum hCG (as needed for women of child bearing potential) to be done at screening and if urine test positive at other time points in the</td></tr>
</table>

Laboratory Assessments	Parameters
	study. • Anti-dsDNA • Rheumatoid Factor • Anti-CCP • ~~Anti-CARP~~ • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula.

Section 9.3.2 Interim Analysis

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK study physician, the study statistician, the study pharmacokineticist, the **PRR DPU Head,** EDL and SRT Leader or designees on an ongoing basis.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with moderate to severe rheumatoid arthritis.

Compound Number: GSK2982772

Development Phase II

Effective Date: 01-APR-2016

Author(s):

PPD

SPONSOR SIGNATORY:

PPD

1st April 2016

Caroline Savage, MD
Vice President & Head Experimental Medicine Unit
Immunoinflammation Therapy Area

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Tel: PPD Mobile: PPD Email: PPD	Mobile: PP	PPD	Pattern Recognition Receptor DPU, UP4440 1250 S Collegeville, PA 19426 USA
Secondary Medical Monitor		Tel: PPD Mobile: PPD Email: PPD	Mobile: PPD		Cytokine Chemokine DPU, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, UK
SAE contact information	Medical Monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

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

Regulatory Agency Identifying Number(s): EudraCT 2016-000912-13

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 203168

Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with moderate to severe rheumatoid arthritis (RA) who are currently being treated with disease modifying anti-rheumatic drugs (DMARDs).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg twice daily for 84 days). In addition to the pharmacokinetics (PK), a number of experimental and clinical endpoints will be employed to obtain information on the pharmacodynamics (PD), and preliminary efficacy in subjects with active RA. Although no formal hypothesis will be tested, these endpoints will enable a broader understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in RA, by making full use of the information obtained from each subject enrolled.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg twice daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg twice daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8 and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on bone and synovial parameters as measured by	• Change from baseline in Magnetic Resonance Imaging (MRI) parameters in the most affected hand/wrist. MRI

Objectives	Endpoints

MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	parameters may include assessment of bone erosions, synovitis, and bone oedema as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system RAMRIQ (Rheumatoid arthritis MRI quantitative) scoring system, and additional exploratory endpoints as data permit.
	• Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:
	  • Exchange rate (K^{trans})
	  • Interstitial volume (V_e)
	  • Plasma volume (V_p)
	  • Initial rate of enhancement (IRE)
	  • Maximal signal intensity enhancement (ME)
	  • Joint volume
	  • Enhancing volume

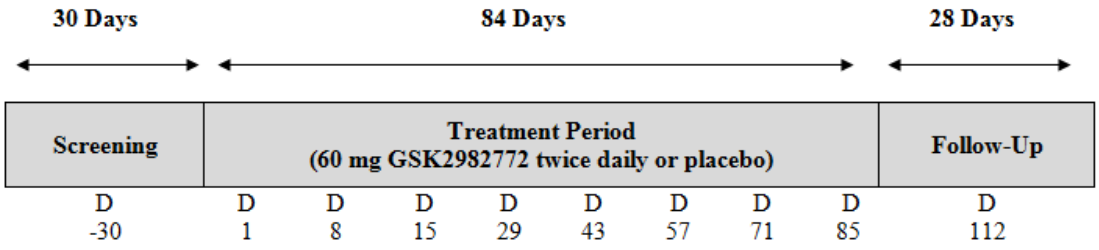
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg twice daily dosing of GSK2982772 on methotrexate (MTX) concentrations.	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue from subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.
• To investigate pathway and target engagement following 60 mg twice daily	• Pharmacology biomarker endpoints may include, but are not limited to the

Objectives	Endpoints
doses of GSK2982772 in blood and synovial biopsy tissue in subjects with moderate to severe Rheumatoid Arthritis.	following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit: • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue. • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg twice daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit.
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on gene expression in the blood subjects with active moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on gene expression in the synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA. The study design schematic is depicted in Figure 1 below.

Figure 1 Study Overview



Key assessments:
Safety assessments, PK samples, DAS28-CRP, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom and Impact Diary, HAQ-DI assessments, MRI, PD samples

Treatment Arms and Duration

Each subject will participate in the study for approximately 20 weeks. This includes a screening period of up to 30 days, an 84 day (12 week) treatment period, and a 28 day follow-up period after the last dose.

Within 30 days of the screening visit (defined as day of consent signing), subjects who are eligible will enter the treatment period and start treatment (or dosing) on Day 1.

The Follow-up Period is 28 days (4 weeks) long. All visits and assessments are detailed in Section 7.1.

Subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

GSK2982772 60 mg twice daily (BID)

Placebo twice daily (BID)

Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 30 subjects with moderate to severe RA are randomised into the study. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor.

Analysis

The safety and tolerability of GSK2982772 following 12 weeks of treatment will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead electrocardiogram (ECG) monitoring.

Ongoing reviews of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GlaxoSmithKline (GSK) individuals, some of who are also members of the GSK study team. The primary purpose of these reviews will be to monitor target engagement, inflammatory markers and Disease activity score for 28 different joints with CRP value (DAS28-CRP) for futility and internal decision making. A data review charter will outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted during the study, when an appropriate number of subjects have completed 12 weeks of treatment or on the request of the DRC. The purpose of this interim will be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in DAS28-CRP will be statistically analysed using a Mixed-effect Model Repeat Measurements (MMRM) comparing GSK2982772 with placebo at each time point.

The relationship between each of the mechanistic endpoints and also with the clinical endpoints may also be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g DAS28-CRP). In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain change in DAS28-CRP (i.e., comparatory rate), based on the data that we have observed in the study. Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

2. INTRODUCTION

2.1. Study Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with moderate to severe rheumatoid arthritis (RA) who are currently being treated with disease modifying anti-rheumatic drugs (DMARDs). All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication type and dose is stable throughout the study.

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg twice daily for 84 days). In addition, a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy in subjects with moderate to severe RA.

2.2. Brief Background

RIP1 is a member of the receptor-interacting Serine/Threonine kinase family containing an amino-terminal kinase domain, an intermediate domain and a carboxy-terminal death domain. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including tumor necrosis factor (TNF) family cytokines, ligands for toll-like receptor (TLR) 3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis [Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008, Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_01]. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and NF-kB-signalling [Ofengeim, 2013, Humphries, 2015]. With this, an inhibitor of RIP1 kinase activity with GSK2982772 may fill a unique niche in the treatment of inflammatory conditions through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a debilitating, progressive polyarthritis that typically affects the small joints of the hands and feet [Vasanthi, 2007]. TNF is known to be one of the key cytokines that drives inflammation in RA [Choy, 2001]. In animal models, transgenic mice that chronically over express low levels of TNF develop a spontaneous polyarthritis that resembles RA in humans [Keffer, 1991] and blockade of NFκB activation results in the development of a spontaneous murine polyarthritis that is RIP1-dependent [Berger, 2014]. In RA patients, TNF is detected in high concentrations in both blood and synovial fluid, and expression of TNF and its signalling intermediates, including RIP1, have been shown to be constitutively increased in PBMCs from RA subjects compared to healthy controls [Raghav, 2006].

Synthetic disease modifying antirheumatic drugs (DMARDs) including nonsteroidal anti-inflammatory drugs, steroids, methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide, are often used alone or in combination in moderate to severe RA; however, most DMARDs do not significantly impact disease progression, and may be hampered by poor side effect profiles. Recently, tofacitinib, an oral small molecule inhibitor of JAK, was approved for moderate to severe RA, but its long term safety is still unknown. TNF antagonists are used in the treatment of patients with moderate-severe disease who have not responded or who have intolerance to traditional DMARDs. While studies have shown that they can improve symptoms and slow the progression of joint damage in many patients [Agarwal, 2011], only half of RA patients achieve American College of Rheumatology (ACR)50 criteria, and many become refractory to anti-TNF

treatments after several years. In addition to the association with increased rates of opportunistic infections across all indications, anti-TNF therapy in RA is linked to lupus-like syndrome and increased rates of demyelinating disease. Other biologic therapies which inhibit T cell activation (abatacept) or lead to selective B cell depletion (rituximab) have shown clinical efficacy in anti-TNF refractory patients, although both carry potential risks for serious infection. Therefore, there remains a high unmet need for safe and tolerable therapies that lead to improved rates of clinical remission and increased physical function in patients with moderate to severe RA.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg twice daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.
Secondary	
• To investigate the plasma concentrations of GSK2982772 following 60 mg twice daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8, and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in MRI parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, and bone oedema as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system RAMRIQ (rheumatoid arthritis MRI quantitative) scoring system, and

Objectives	Endpoints

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

• To investigate the effect of 60 mg twice daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg twice daily dosing of GSK2982772 on methotrexate (MTX) concentrations	• Plasma concentrations of MTX pre-dose GSK2982772 onDays 1, 8, and 43 (Week 6).
Exploratory	
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.
• To investigate pathway and target engagement following 60 mg twice daily doses of GSK2982772 in blood and synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit: • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue.

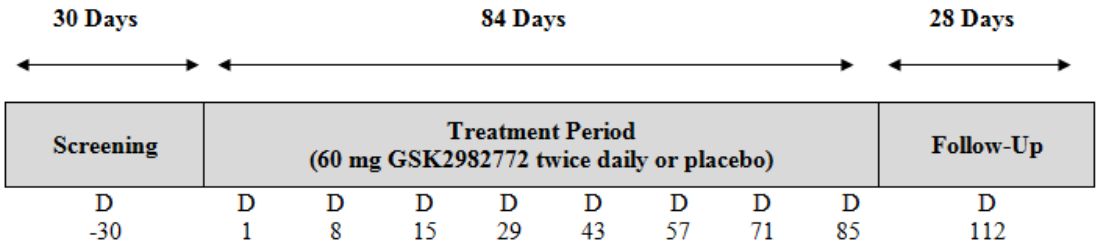
Objectives	Endpoints
	• Total or phosphorylated RIP1, MLKL, andRIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg twice daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on gene expression in the blood of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg twice daily doses of GSK2982772 on gene expression in synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

4. STUDY DESIGN

4.1. Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA. The study design schematic is depicted in Figure 2 below.

Figure 2 Study Overview



Key assessments:
Safety assessments, PK samples, DAS28-CRP, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom and Impact Diary, HAQ-DI assessments, MRI, PD samples

4.2. Treatment Arms and Duration

It is anticipated that the total duration of participation in the study will be approximately 20 weeks from screening to the last study visit.

4.2.1. Screening

Within 30 days of the screening visit (defined as day of consent signing), subjects who are eligible will enter the treatment period and start treatment (or dosing) on Day 1.

4.2.2. Treatment Period

Subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally twice daily (approximately 12 hours apart) for 84 days (12 weeks). Further guidance and information for study treatment and dosing are provided in the Study Reference Manual (SRM).

During the 84 day (12 week) treatment period, subjects will attend the clinical site for visits on Days 1, 8, 15, 29, 43, 57, 71 and 85. At specific visits, subjects must not take study treatment prior to their scheduled visit (see Section 7.1). On Days 22, 36, 50, 64 and 78, each subject will be contacted by telephone and asked about their general health. Subjects will be given a diary card at each of the visits on which they will be instructed to

record their daily study medication and concomitant medication taken and any adverse events.

4.2.3. Follow-up Period

After the Treatment Period, the subject will enter the Follow-up Period which lasts for 28 days post the last administration of study medication, in order to complete follow-up assessments per the Time and Events Table (see Section 7.1).

4.3. Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 30 subjects with moderate to severe RA are randomised into the study. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor.

4.4. Design Justification

As this is the first trial of GSK2982772 in subjects with RA, the primary endpoint is the safety and tolerability of GSK2982772. In addition, this study will include assessments of target engagement and downstream PD effects of GSK2982772, to understand whether GSK2982772 is inhibiting the pathway of interest in this disease.

The 12 week duration of treatment is based on review of previous proof of mechanism and proof of concept studies in RA and is limited by the supporting 13 week toxicology studies. It is expected that an effective therapy should cause group level changes in the mechanistic parameters by the 12 week time point.

The subjects will be randomised in a 2:1 ratio to GSK2982772 60 mg twice daily (BID) and placebo respectively. The primary objective of this study is to assess safety and tolerability, and assessment of this is most valuable in a placebo controlled study. The placebo group was also deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. All subjects will be allowed to continue standard of care therapy including non-biologic DMARDs during the study, provided that the medication and dose is stable throughout the study.

4.5. Dose Justification

The selection of the 60 mg BID dose to be tested in this study is based on the safety, PK, and PD data from the First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2h). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose is predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects will have >90% target engagement in blood at C_{min}. No data are currently available about the distribution of GSK2892772 into the synovium. Based on data in non-steroidal anti-

inflammatory drugs (NSAIDs), the synovial fluid concentrations fluctuate to a much lesser extent than those in plasma [Netter, 1989]. Peak drug concentrations are generally lower in synovial fluid but are similar to plasma at later time points. Assuming the same is true for GSK2982772, a 60 mg BID dose should provide similar RIP1 target engagement at the site of action as predicted in blood.

Therefore, it is predicted that a dose of GSK2982772 60 mg BID may be clinically efficacious in subjects with RA.

It is anticipated that a human dose of 60 mg will produce area under the concentration-time curve ($AUC_{[0-24]}$) and maximum observed concentration (C_{max}) values of approximately 9 µg.h/mL and 1 µg/mL, respectively, which are approximately $1/6^{th}$ and $1/12^{th}$ of the gender-averaged AUC (48.4 µg.h/mL) and C_{max} (12.3 µg/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the IB [GlaxoSmithKline Document Number 2014N204126_01]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2982772		
Central Nervous System (CNS) effects	**Non-clinical data**: In the 4-week GLP toxicology study, CNS findings were observed in 4/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance, and decreased activity. The clinical relevance of these findings in humans is not known. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical data**: A First Time in Human (FTiH) study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date. See Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_01]. No drug-associated CNS adverse events were identified and no Serious Adverse Effects (SAEs) were reported.	**Subject Selction**: • Subjects with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening. **Subject Monitoring**: • Subjects will be monitored for standard CNS-related adverse events.
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids.	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, HIV, Hepatitis B and C, and excluded from the study if positive.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: In the FTiH study, no SAEs were reported. One subject experienced an Adverse Effect (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded Investigator determined this to be potentially drug-related.	**Subject Monitoring**: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 5.4.1).
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in subjects wtih RA.
Respiratory	**Non-clinical data**: In the single dose Safety Cardiovascular (CV) and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (minute volume) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related adverse events. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK2982772 [GlaxoSmithKline Document Number 2014N204126_01]. **Clinical data**: In the FTiH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related adverse events were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based upon pre-clinical studies. **Clinical data**: In the FTiH study, there have been some reports of lethargy, abnormal dreams, and depressed mood. No events of suicidal ideation or behaviour or changes in behaviour were reported.	**Subject Selection**: • Subjects with a current history of suicidal ideation and behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel using the (Columbia Suicide Severity Rating Scale) C-SSRS in all subjects. See Section 7.3.7.
Reproductive toxicity	**Non-clinical data:** In an early rat embryofetal development study, there was no maternal or developmental toxicity at doses ≤ 200 mg/kg/day. In a rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection**: • Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 30 days (females) and 90 days (males) after the last administration of study drug (Appendix 6).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing uptake of OAT3 were completed. There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. MTX is an OAT3 substrate in which GSK2982772 could potentially impair the clearance of MTX.	**Subject Monitoring:** • PK sample collection to evaluate the potential interaction of GSK2982772 and MTX will be performed thoroughout the study. • Subjects should be monitored for potential effects of interaction between GSK2982772 and MTX. • Clinical laboratory results (e.g., liver function tests) are routinely being monitored throughout the study.
Study Procedures		
Synovial Joint Biopsy	Potential risks of the procedure include discomfort, infection or bleeding. **Note**: Synovial biopsies are optional and not required on all subjects.	**Subject Selection:** • Subjects with known allergy to lidocaine or other local anaesthetics will not be included in the biopsy portion of the study. • Subjects with a platelet count $\leq 100 \times 10^9$/L will be excluded from participation. **Subject Management**:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• The biopsies will be performed under ultrasound or arthroscopic guidance. Subjects will be given instructions for aftercare and contact information should there be any adverse reactions after the procedure. • Biopsy site healing will be monitored during the study as part of AE safety review.
Gadolinium (Gd) containing MRI contrast agents	**Non-clinical data**: Animal studies have shown reproductive toxicity of gadolinium (Gd)-containing MRI contrast agents at repeated high doses. **Clinical data**: Use of MRI contrast agents in subjects with severely impaired rental function (GFR<30mL/minute) has been associated with Nephrogenic Systemic Fibrosis (NSF). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed against the risks. Gadolinium (Gd) contrast agents can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory, or cutaneous manifestations, and ranging to severe reactions including shock. In general, subjects with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions. The risk of hypersensitivity reactions may be higher in cases of: • Previous reaction to contrast media • History of bronchial asthma • History of allergic disorders	**Subject Selection:** • Pregnant or lactating females will be excluded from taking part in the study. • Subjects with impaired renal function (GFR<60mL/minute) are excluded by the eligibility criteria. • Subjects with history of sensitivity to Gd-containing contrast agents will be excluded from the study. The MRI procedure will be conducted under the supervision of trained and qualified clinical staff that is trained to appropriately manage an allergic reaction. • Sites will be responsible for following any additional safety information for the specific Gd contrast agent used at their site and not enroll subjects if contraindicated. **Subject Monitoring and Management**: • MRI contrast at a dose less than or equal to 0.1 mmol/kg per imagining session at baseline and Days 43 and 85 will be used in the MRI protocol. • Effective contraception is required during the study, and pregnancy testing will be performed regularly throughout the study and prior to dosing in females of child bearing potential.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely observed.	
Other		
Exposure to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner.	**Subject Selection:** • All participants will be screened according to local hospital criteria and study inclusion/exclusion before entering the MRI scanner to ensure they are able to have the MRI conducted. Subjects with non-magnetic resonance compatible metal implants or implantable electronic devices (e.g., pacemaker, defibrillator) will not be included in this study.

4.6.2. Benefit Assessment

There are additional treatment options available for subjects who have an inadequate response to current therapies for RA. It is possible that treatment with GSK2982772 may be effective in the treatment of RA, as the FTiH study demonstrated that the drug engaged with the target and produced *ex vivo* PD effects in suppression of RIP1-dependent cytokines MIP1α and MIP1β [GlaxoSmithKline Document Number 2014N204126_01]. There will be limited direct benefit to the subject through their contribution to the process of developing new therapies in an area of unmet need.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded to patients with RA by contributing to the understanding of the disease and the development of new therapies for patients with these conditions in the future.

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 (IP) or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number 2014N204126_01].

In addition, Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including vaccinations for influenza and pneumococcus, in subjects with RA.

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

5.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects that do not have any medical conditions, other than moderate to severe RA, that in the opinion of the Investigator put the subject at unacceptable risk or interfere with study assessments or integrity of the data. These medical conditions should be

stable at the time of screening and are expected to remain stable for the duration of the study.

3. Subject has had a confirmed diagnosis of rheumatoid arthritis according to the revised 2010 American College of Rheumatology/European League Against Rheumatism ACR-EULAR classification criteria.
4. Disease duration of ≥ 12 weeks (time from onset of patient-reported symptoms of either pain or stiffness or swelling in hands, feet or wrists) at screening.
5. Swollen joint count of ≥4 (28-joint count) and tender joint count ≥ 4 (28-joint count) at screening.
6. Subject has a DAS28 CRP disease activity score of ≥ 3.2 and CRP ≥ 5.0 mg/L (≥4.76 nmol/L) at screening.
7. Subject must have received at least 12 weeks of non-biologic DMARD monotherapy or methotrexate (MTX)/DMARD combination therapy prior to screening AND must be on stable dose throughout the study.
8. Subject is naive to any biological therapies for RA

   OR

   Subject may have had previous exposure to a single anti-TNF biologic agent which was discontinued for reasons other than primary non-response more than 8 weeks (or 5 half lives whichever is longer) from first dose. **Note: Exposure to a single anti-TNF is not required in addition to Inclusion #7 above.**
9. For subjects who have consented to synovial joint biopsy:
   a. Subject has an involved knee, wrist, or ankle suitable for biopsy, as assessed by a rheumatologist at screening.

WEIGHT
10. A body mass index (BMI) within range of 18.5 - 35 kg/m^2 (inclusive) at screening.

SEX
11. Male and female subjects **Males:** Male subjects with female partners of child bearing potential must comply with the following contraception requirements in Appendix 6. **Females**: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential as defined in Appendix 6. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 6) from 30 days prior to the first dose

of study medication and until at least 30 days after the last dose of study medication and completion of the follow-up visit.

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

INFORMED CONSENT
12. 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. Subject with a positive anti-double stranded deoxyribonucleic acid (DNA [anti-dsDNA]) and confirmed diagnosis of systemic lupus erythematosus (SLE). 2. Subject with current history of Suicidal Ideation Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide. 3. An active infection, or a history of infections as follows: • Hospitalisation for treatment of infection within 60 days before first dose (Day 1). • Currently on any suppressive therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria). • Use of parenteral (IV or intramuscular) antibiotics (antibacterials, antivirals, antifungals, or antiparasitic agents) for an infection within 60 days before first dose. • A history of opportunistic infections within 1 year of screening (e.g. pneumocystis jirovecii, CMV pneumonitis, aspergillosis). This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or recurrent nature. • Recurrent or chronic infection or other active infection that, in the opinion of the Investigator might cause this study to be detrimental to the patient. • History of TB, irrespective of treatment status. • A positive diagnostic TB test at screening defined as a positive QuantiFERON-TB Gold test or T-spot test. In cases where the QuantiFERON or T-spot test is indeterminate, the subject may have the test repeated once, but they will not be eligible for the study unless the second test is negative. In cases where the QuantiFERON or T-spot test is positive, but a locally-read follow up chest x-ray, shows no evidence of current or previous pulmonary

tuberculosis, the subject may be eligible for the study at the discretion of the Investigator and GSK Medical Monitor.

4. QTc > 450msec or QTc > 480msec for subjects with bundle branch block at screening.

   The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual over read.

   The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined and documented prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
5. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
6. Current active or chronic history of liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. Current or history of renal disease or estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 mL/min/1.73m^2 at screening.
8. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
9. A major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
10. Any planned surgical procedures including surgical joint procedures (e.g., intra-articular, tendon sheath, or bursal corticosteroid injections) during the study.
11. A history of malignant neoplasm within the last 5 years, except for adequately treated non-metastatic cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix that has been fully treated and shows no evidence of recurrence.
12. Has undergone surgery including synovectomy or arthroplasty on the joint chosen for biopsy and/or magnetic resonance imaging (MRI).
13. The subject has a history of any other joint disease other than RA at the knee, wrist or ankle joint chosen for biopsy and/or MRI (e.g., gout, pseudogout, osteoarthritis).
14. Has undergone intra-articular corticosteroid injection, arthrocentesis or synovial biopsy on any joint within 6 weeks of screening.
15. A known allergy to lidocaine or other local anaesthetics (**Note**: only applies to subjects who consent for synovial biopsy procedures).
16. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but are not limited to:
    - Intracranial aneurysm clips (except Sugita™) or other metallic objects,
    - History of intra-orbital metal fragments that have not been removed by a medical professional.
    - Pacemakers or other implanted cardiac rhythm management devices and non-MR compatible heart valves,

- Inner ear implants,
- History of claustrophobia which may impact participation.

CONCOMITANT MEDICATIONS
17. The subject has received treatment with the therapies listed in Section 6.11.2, or changes to those treatments, within the prescribed timeframe. If in doubt, or the therapy is not listed please consult with the medical monitor. • 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
18. History of alcohol or drug abuse that would interfere with the ability to comply with the study.

CONTRAINDICATIONS
19. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation. 20. Received a live or attenuated vaccine within 30 days of randomization OR plan to receive a vaccination during the study until half-lives (or 2 days) plus 30 days after receiving GSK2982772. 21. Contraindication to gadolinium contrast agent in accordance with local guidelines. 22. The subject has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer before the first dose of study medication, or plans to take part in another clinical trial at the same time as participating in this clinical trial.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
23. Haemoglobin <11 g/dL;haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x 10^9/L) or ≥14,000/mm^3 (≥14 x 10^9/L); platelet count ≤ 100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤3 x 10^9/L; lymphocyte count <1 x 10^9/L at screening. 24. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. As potential for and magnitude of immunosuppression with this compound is unknown, subjects with presence of hepatitis B core antibody (HBcAb) should be excluded. 25. A positive serology for human immunodeficiency virus (HIV) 1 or 2 at screening. 26. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months. 27. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dose.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events and protocol deviations (see Section 7.3.1.5).

Subjects who do not qualify to participate in the study due to a screening laboratory value or ECG abnormality can repeat the test once within the original screening window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

Subjects can be re-screened only on approval of the GSK Medical Monitor and only once. Re-screening is allowed when a subject failed inclusion/exclusion criteria or some other screening condition initially, but the Investigator believes there is a reasonable probability that the subject would be eligible if re-screened.

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 Case Report Form (CRF).
- The Sponsor's request, for reasons such as significant protocol deviations (and after discussion with the Investigator).
- If a subject is withdrawn from study treatment, this subject is also considered to be withdrawn from the study.
- Study is terminated by the Sponsor.

If a subject is withdrawn, the Sponsor may decide to replace that subject and this will be done through the Interactive Response Technology System (IRTS).

If a subject chooses to withdraw from the study after dosing then the Investigator must make every effort to complete the follow-up assessments detailed in the Time and Events Table (Section 7.1).

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

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.

- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

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 medications for the treatment of RA as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or Haematologic stopping criteria (Section 5.4.5) are met.

5.4.2. Group Safety Stopping Criteria

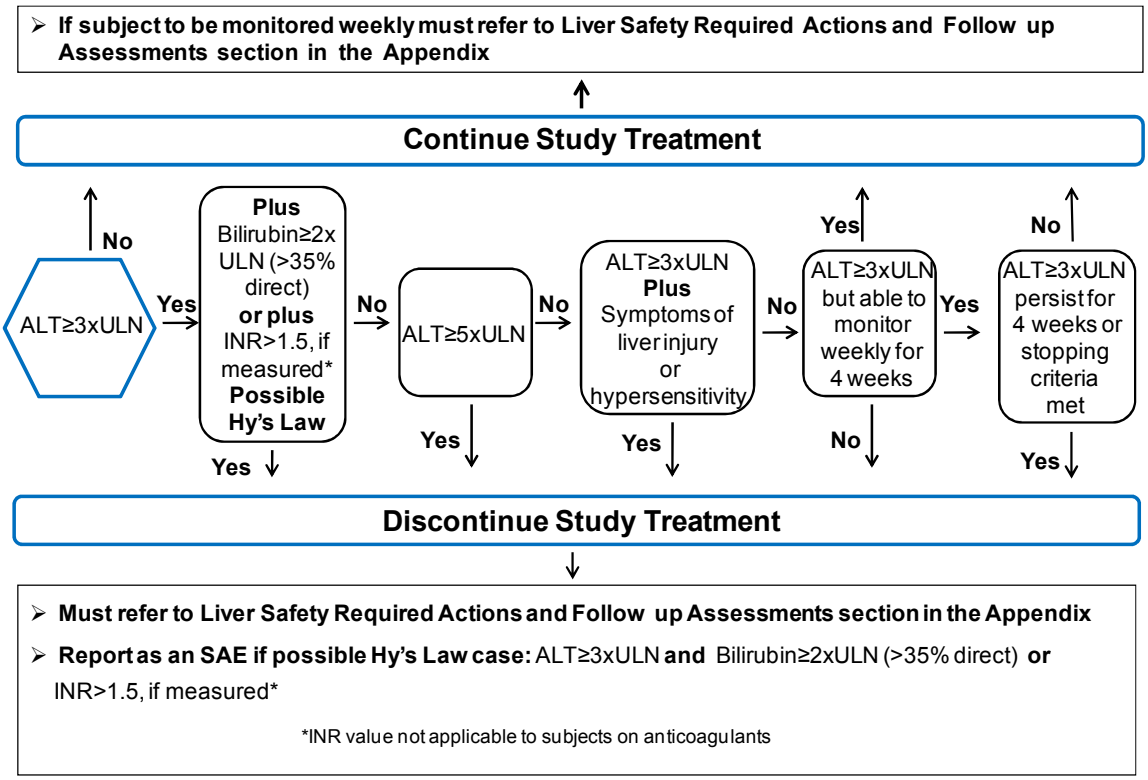
In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subjects will be regularly reviewed by the Sponsor Safety Review Team (SRT) in order to ensure appropriate subject safety. Any changes to the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

5.4.3. 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

Figure 3 Phase II Liver Chemistry Stopping Criteria – Liver Stopping Events Algorithm



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

5.4.3.1. 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.

5.4.4. QTc Stopping Criteria

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

- 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 decision to withdraw a subject will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.4.5. 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 $\geq$ 3 g/dL from baseline (pre-dose Day 1)
- Neutrophils $<1 \times 10^9$/L
- Lymphocytes $<0.5 \times 10^9$/L
- Platelets $<50 \times 10^9$/L

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 study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treamtent	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions:	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Physical description:	White to almost white, round, film coated tablet	White to almost white, round, film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

6.2. Treatment Assignment

At Screening a unique Subject Number will be assigned to any subject who has signed a consent form. The unique Subject Number will be used to identify individual subjects during the course of the study. Any subject that is re-screened outside of the allowed screening window at the approval of the GSK Medical Monitor, must be assigned a new unique Subject Number .

Subjects who meet screening eligibility criteria will be randomised to a treatment group through an Interactive Response Technology System (IRTS). The IRTS will confirm the subject's CRF number (Subject Number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other subject in the study.

Therefore, the randomisation is centrally controlled by the IRTS.

Subjects will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio.

6.3. Planned Dose Adjustments

No dose adjustments are allowed.

6.4. Blinding

This will be a double blind (sponsor unblinded) study and the following will apply:

- Sponsor unblinded refers only to the Data Review Committee, consisting of the GSK study physician, study statistician, study pharmacokineticist, Early Development Lead (EDL) and Safety Review Team (SRT) Leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.
- The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator. Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject to his/her study staff or GSK, 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.
- A subject will be withdrawn if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (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.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing.

When subjects self-administer study treatment(s) at home, compliance with GSK2982772 and placebo will be assessed and documented through the review of the subject's diary card and querying the subject during the site visits. A record of the number of GSK2982772 or placebo tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

Subjects will be given instructions on compliance and treatment with MTX (if applicable). The date, time and total weekly dose will be recorded in the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 > 120 mg daily will be considered an overdose. GSK does not recommend specific treatment for an overdose. The Investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

In the event of an overdose, the Investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) for at least 48 hours following the last dose of GSK2982772.
3. Obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document all details of the overdose 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

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

Subjects will not receive any additional treatment from GSK after completion of the study because the 12 week duration of treatment is limited by the supporting 13 week toxicology studies.

6.10. Lifestyle and/or Dietary Restrictions

- Subjects must adhere to the contraceptive requirements listed in Appendix 6.

6.10.1. Activity

- Subjects will abstain from strenuous exercise more than their normal routine for 48 hours prior to each blood collection for clinical laboratory tests.
- Subjects who have consented to synovial biopsies will abstain from strenuous exercise for 24 hours after synovial biopsy procedures.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Selected medications for the treatment of RA may be taken, with specific requirements listed in Table 1, and as long as they are not prohibited (Section 6.11.2). All concomitant medications taken during the study will be recorded in the source document and CRF. The minimum requirement is that drug name and dates of administration are recorded.

Table 1 Specific Requirements for Permitted Medications During the Study

Drug	Requirement
Methotrexate	Stable dose regimen (up to 25 mg/week) for at least 12 weeks prior to screening and remain on this dose throughout the study (unless dose must be reduced because of a safety concern). MTX should be taken on the same day of week and at approximately the same time of day throughout the study.
Sulfasalazine	Stable dose regimen for at least 12 weeks prior to screening and throughout the study.
Hydoxychloroquine or cholorquinine	Stable dose for at least 12 weeks prior to screening and throughout the study.
Leflunomide	Stable dose for at least 12 weeks prior to screening and throughout the study.
Folate supplements (minimum of 5 mg/week)	If a subject is on folate supplements with MTX treatment, they must be on a stable dose regimen for at least 4 weeks prior to randomization and throughout the study.
Other oral anti-rheumatic therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticords (e.g., prednisolone ≤ 10 mg /day. See Appendix 3 for equivalent doses).	Stable dose regimen for at least 4 weeks prior to screening and throughout the study (unless reduction required due to adverse effects). Omit dose on the morning prior to study visits until after joint assessments.

6.11.2. Prohibited Medications and Non-Drug Therapies

Table 2 lists prohibited medications for defined periods of time before and during the study until after the follow up visit.

Subjects who start prohibited medications or therapies as a treatment for RA or other reasons during the study will be withdrawn from study treatment for safety reasons. If in any doubt, Investigators are advised to discuss medications with the medical monitor.

Table 2 Prohibited Medications

Therapy	Time period
A change in dose of methotrexate or other DMARD.	12 weeks prior to screening until after the follow up visit (Day 112)
Greater than 10mg/day oral prednisolone (or equivalent glucocorticoid) or a change in dose of corticosteroid.	4 weeks prior to screening until after the follow up visit (Day 112)
Intramuscular glucocorticoids (e.g., methylprednisolone ≤120 mg/month)	4 weeks prior to screening until after the follow up visit (Day 112)
Intra-articular corticosteroid injections	6 weeks prior to screening and until after the follow up visit (Day 112).
Biologic therapies for the treatment of rheumatoid arthritis not limited to anti-TNF biologics or other biologics, rituximab, anakinra, abatacept or tocilizumab.	At any time
Exposure to more than one anti-TNF biologic therapies for the treatment of RA including but not limited to anti-TNF biologics, infliximab, adalimumab, etanercept, certolizumab and golimumab. **Exception**: Exposure to a single anti-TNF-biologic for which the subject discontinued for a reason other than primary non-response is permitted.	Cannot have been exposed to more than one anti-TNF biologic or be on at any time during the study. In the case of a single anti-TNF biologic for which the subject discontinued for a reason other than primary non-response, the subject must not be on for 8 weeks or 5 ½ lives (whichever is longer) prior to first dose until after the follow up visit (Day 112).
Live vaccination	Live or attenuated vaccinations are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered whilst receiving GSK2982772 based on an assessment of the benefit:risk (e.g., risk of decreased responsiveness). Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in subjects with RA.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM and laboratory manual. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

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

- At study visits, the Patient Reported Outcomes (PROs) should be completed prior to any other study assessments.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak 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.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- 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.

7.1. Time and Events Table

Procedures	**Screening (-30)**	**Treatment Period[17]**													**Early Withdrawal[18]**	**Follow Up (±3)[19]**
		Day 1	**Day 8 (±3)**	**Day 15 (±3)**	**Day 22 (±3)**	**Day 29 (±3)**	**Day 36 (±3)**	**Day 43 (±3)** (week 6)	**Day 50 (±3)**	**Day 57 (±3)**	**Day 64 (±3)**	**Day 71 (±3)**	**Day 78 (±3)**	**Day 85 (+2)** (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------X															
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4]						X[4]						X	X[16]	

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
Study Treatment																
Randomisation		X														
Study medication (twice daily)[8]		X----------												----------X		
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB,Hep C Ab, Anti-CCP, Anti-dsDNA, Anti-CARP, RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers, mRNA, and TE[11]		X[4]						X[4]						X	X	
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4]						X[4]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. 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. AEs will be collected from the start of Study Treatment until the follow-up contact.
6. All PRO assessments should be conducted before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist.
8. Subjects must take study medication twice a day approximately 12 hours apart. Exact time of dosing to be recorded in diary cards. On Days 8,43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71.
11. Blood samples for inflammatory biomarkers, mRNA and target engagement . See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or at Early Withdrawal .
13. PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX must take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits must be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Witdrawal visit .
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days ($\pm$3 days) after the last dose of study medication.

7.2. Screening and Critical Baseline Assessments

After written informed consent, screening assessments will be performed as outlined in the Time and Events Table (Section 7.1).

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

Medical/medication/family history, ECG and laboratory tests 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.

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

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The Investigator will be responsible for determining the clinical significance of any results that fall outside of the laboratory normal ranges.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT), which will include 203168 study team members, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

7.3.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 5.

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the time points specified in the Time and Events Table (Section 7.1).

- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.3.1.2. Method of Detecting AEs and SAEs

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

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

7.3.1.3. 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 stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5and 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.

7.3.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.3.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 30 up to 90 days (as applicable) after the last dose.
- If a pregnancy is reported within 30 days (90 days in partners) after the last dose then the Investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the head, eyes, ears, nose, throat, skin, thyroid, joint, lymph nodes, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded at the first physical examination.
- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.3.4. Vital Signs

- Vital signs will be measured in semi-supine position after approximately 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

7.3.5. Electrocardiogram (ECG)

- Triplicate12-lead ECGs will be obtained at screening and single 12-lead ECGs obtained at every time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F or B) intervals. Refer to Section 5.4.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period.
- ECG to be measured in a semi-supine position after approximately 5 minutes rest.

7.3.6. Clinical Safety Laboratory Assessments

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

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

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

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

- Haematology, platelets and coagulation sample if they are required to be taken closer to the biopsies (as per local practices) than specified in Section 5.4.5.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology [1,2]	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [3]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose[4]	Calcium	Alkaline phosphatise	Albumin
	CRP	Triglycerides[4]	Total Cholesterol[4]	Fasting HDL cholesterol[4]
	Fasting LDL cholesterol[4]			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening and RoutineTests	• HIV 1 & 2 • Hepatitis B (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis C (Hep C antibody) • QuantiFeron Gold Test • T-spot (if QuantiFeron is indeterminant) • FSH and estradiol (as needed in women of non-child bearing potential only) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [5] • Serum hCG (as needed for women of child bearing potential) to be done at screening and if urine test positive at other time points in the study. • Anti-dsDNA • Rheumatoid Factor • Anti-CCP • Anti-CARP • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula.			

Footnotes:

1. The subject's CBC results from the previous scheduled visit should be checked prior to the synovial biopsy

procedures according to local practices and may be repeated at the discretion of the investigator.
2. Details of Haematologic Stopping Criteria are given in Section 5.4.5.
3. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.3 and Appendix 2.
4. No fasting required. Any abnormal result for glucose or lipids (non-fasted) may be repeated at the discretion of the Investigator.
5. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

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

7.3.7. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with RA. Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. Consideration should be given to discontinuing GSK2982772 in subjects who experience signs of suicidal ideation or behaviour.

Families and caregivers of subjects being treated with GSK2982772 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study Investigator.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening CSSRS' will be completed. At Days 43 (Week 6) and 85 (Week 12), the 'Since Last Visit CSSRS' will be completed. GSK Version 4.1 of both rating scales will be used.

Subjects who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their GP or appropriate psychiatric care. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 7.3.1 AE and SAE). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

7.4. Efficacy

7.4.1. Patient Reported Outcomes

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

7.4.1.1. Rheumatoid Arthritis Symptoms and Impact Diary

Symptoms associated with RA will be assessed using a novel RA Symptom and Impact Diary as per Section 7.1, Time and Events Table. The study staff should not clarify any of the questions for the subject.

7.4.1.2. Patient Assessment of Joint Pain

The severity of the subject's joint pain will be assessed by completion of a numeric rating scale (NRS). The subject will be asked to select a whole number (0-10 integers) that best reflects the intensity of their pain. The scale is represented by a horizontal bart with "no pain" at the lower anchor and "most severe pain" at the upper anchor. This questionnaire should take approximately 1 minute to complete.

The patient assessment of joint pain will be used to calculate ACR responders.

7.4.1.3. Patient's Global Assessment of Disease (PtGA)

Subjects will complete a global assessment of disease activity using the patient global assessment item, a visual analogue scale (VAS) with anchors "0" (very well) to "10" (very poor).

The patient's global assessment of disease will be used to calculate DAS clinical scores and ACR responders.

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

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.

This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas [Fries, 1980]:

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

Responses are scored from 0 (no difficulty) to 3 (inability to perform a task in that area).

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

7.4.1.5. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale

Subjects will complete a 13-point fatigue questionnaire using the FACIT-Fatigue assessment, a Likert scale from 0 to 4, to "0" (very much fatigued) to"4" (not at all fatigued). This questionnaire should take a few minutes to complete and provides the level of fatigue with usual daily activities from the previous week.

7.4.2. Clinical Disease Assessments

Brief details are given below and detailed procedural instructions are given in the SRM. The sponsor will calculate DAS28(CRP) and ACR (20/50/70) responses at each assessment time point as defined below.

7.4.2.1. Disease Activity Score (DAS) Assessments

The DAS28 is a measure of disease activity. It is a composite score derived measurement weighing given to each component.

The components of the DAS28 assessment include:

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

7.4.2.2. American College of Rheumatology Criteria (ACR) Assessments

The ACR Criteria is a standard criteria to measure the effectiveness of treatments from placebo. The ACR's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvement.

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

- Tender/Painful Joint count (28)
- Swollen Joint Count (28)
- Patient Assessment of Joint Pain
- PtGA
- PGA
- CRP
- HAQ-DI

7.4.2.3. Joint Assessments

Tender Joint Count Assessments
A total of 28 joints will be scored for presence or absence of tenderness.

Swollen Joint Count Assessments

A total of 28 joints will be scored for presence or absence of swelling.

Joint assessments will be used to calculate DAS28 clinical scores and ACR responders.

7.4.2.4. Measurement of Serum CRP

Blood samples will be collected in order to measure serum CRP concentrations. The CRP is a component of the DAS28, ACR, and Vectra DA clinical scores.

7.4.2.5. Physician's Global Assessment of Disease Activity (PGA)

The Investigator or physician designee only will complete a global assessment of disease activity using the physician global assessment item, a VAS with anchor's "0" (none) to "10" (extremely active).

Note:

- The Investigator or physician designee should complete the PGA independently of the subject.
- Ideally, the same Investigator or physician designee should perform all global assessments for each subject during the duration of the study.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for PK analysis of GSK2982772 will be collected at the time points indicated in Section 7.1 Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

For subjects who are on stable doses of methotrexate (MTX), blood samples for PK analysis of MTX will be collected at the time points indicated in Section 7.1 Time and Events Table. The actual date and time of each blood sample collection will be recorded.

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

7.5.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technologies and Science In vivo In vitro Technology (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of

GSK2982772 and MTX will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma sample has been analysed for GSK2982772 any remaining plasma sample may be analysed for other compound-related material and the results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.5.3. Synovial Biopsy Tissue for Pharmacokinetic Assay

See Section 7.6.2.2 for details on synovial tissue biopsy and procedure. If available, synovial tissue samples may be analysed for concentrations of GSK2982772 and possible drug-related material, as well as specific tissue distribution if feasible as sample availability allows.

7.5.4. Sample Analysis

Synovial biopsy sample analysis will be performed under the control of PTS IVIVT, GlaxoSmithKline. Information on processing the biopsies for the synovial pharmacokinetic assay will be provided in the laboratory manual. The results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.6. Biomarker(s)/Pharmacodynamic Markers

Pharmacodynamic biomarkers will be collected at the time points in Section 7.1 Time and Events Table and may include, but are not limited to, the following:

- Blood samples for mRNA expression e.g., IL6, MMP-1, MMP3, MMP-13, TIMP-1, MCP-1 and MIF.
- Blood samples for biomarkers which may be indicative of RA disease activity e.g., MRP8/14 and markers encompassed by Vectra DA.

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

7.6.1. Magnetic Resonance Imaging (MRI) of Joint

The most affected hand will be documented at baseline and used for all imaging visits. If subjects report both hands are equally involved, then the subject's dominant hand will be used.

DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability, only a standard MRI will be performed.

Each subject's most affected wrist (corresponding to the affected hand which is determined and documented at baseline) will be imaged by MRI at pre-dose on Days 1, 43 and 85 (see Section 7.1). If a scanning failure occurs at any visit, if feasible a rescan is allowed within 7 days after the failed scan after consultation and agreement with the

GSK Medical Monitor. There will be a minimum of 24 hours between scans where gadolinium (Gd) contrast is used. The MRI will be used in order to non-invasively quantify the degree of inflammation and structural changes within the target joint.

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

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

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

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

7.6.2. Synovial Biopsy

7.6.2.1. Selection of Joint for Synovial Biopsy

Synovial biopsies are optional for subjects enrolled in this study. There is no minimum number of subjects with joint biopsies required, but biopsies should be performed in as many subjects as possible. Synovial biopsy of a subject's swollen and tender wrist, knee or ankle joint will be performed at baseline (pre-dose Day 1). The final choice of joint is left to the discretion of the Investigator, although ideally it will be the most inflamed joint. The same joint should be biopsied at Day 43 (Week 6). If in the event that a repeat biopsy of the same joint as baseline is not possible, the joint may change if essential, after discussion with the GSK Medical Monitor. Any change must be documented in the CRF.

If a subject chooses to withdraw from the study after dosing and prior to Day 43, the Investigator must make every effort to perform a synovial biopsy if the subject has received at least 14 days of treatment with GSK2982772 or placebo.

7.6.2.2. Synovial Biopsy Procedure

Ultrasound imaging or arthroscopy will be used to guide the collection of approximately (as feasible for any given subject) of 6 synovial biopsies for immunohistochemistry (IHC), 6 synovial biopsies for pharmacokinetics, 6 synovial biopsies for target engagement, and 6 synovial biopsies for RNA extraction up to a combined maximum of 30 biopsies from the chosen joint under local anaesthesia (see SRM).

Biopsy tissue taken from synovial tissue will be divided accordingly for IHC, PK, target and pathway engagement, and gene expression. Histological assessment by IHC will be evaluated for general appearance and total inflammatory infiltrate. Specific cell numbers will also be analysed (which may include but are not limited to CD3+T-cells, CD55+ fibroblast-like synoviocytes, CD68+macrophages). mRNA may be isolated from synovial biopsys tissue, as feasibility dictates, to determine the effect of placebo and GSK2982772 on markers of inflammation and tissue healing (e.g., may include and not be limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1 and other chemokines and cytokines). Biopsy tissue collected for RNA transcriptional analysis may be utilised to determine the effect of GSK2982772 on cytokine and receptor expression, in addition to other markers of inflammation and tissue healing, as feasibility allows. For example, this may include but is not limited to, measurement of acute phase proteins, other chemokines and cytokines. Examples of technologies that may be used for these analysis include, but are not limited to, quantitative PCR, microarray, RNA sequencing or mass cytometry (CyTOF).

7.6.3. Novel Pharmacodynamic Biomarkers

7.6.3.1. RIP1 Target Engagement in Blood

Blood samples for RIP1 target engagement will be collected at the time points indicated in Section 7.1 to measure levels of free and drug-bound RIP1 protein.

7.6.3.2. RIP1 Target Engagement in Synovial Tissue

Synovial tissue biopsy samples will be collected at the time points indicted in Section 7.1 to measure levels of free and drug-bound RIP1 protein if sample quantity and data allow.

7.6.3.3. Pathway Biomarkers in Synovial Tissue

Synovial tissue biopsy samples will be collected at the time points indicated in Section 7.1 to measure total or phosphorylated RIP1, RIP3, MLKL and cleaved or total caspase 3 and caspase 8 if sample quantity and data allow.

7.6.4. Exploratory Novel Biomarkers

With the subject's consent, tissue and blood sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence disease/condition for study treatment, and/or medically related conditions, as well as the biological and clinical responses to GSK2982772. 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 GSK2982772 may be identified by application of:

- Gene expression analysis may be conducted on the blood and/or synovial biopsies using microarray, RNA sequencing and/or alternative equivalent technologies, which facilitates the simultaneous measurement (and confirmation) of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each synovial tissue sample.
- Soluble inflammatory mediators in the blood may be assayed for cytokine and inflammatory mediators including, but not limited to, pro-inflammatory and anti-inflammatory cytokines, chemokines, and acute phase proteins.

These analyses may be reported under separate protocol following the completion of the study. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

7.7. Genetics

In consenting subjects, a blood sample for pharmacogenetics (PGx) research will be drawn on Day 1 (or any time point post randomisation and prior to study completion) to better characterize genetic variability that may affect efficacy or safety endpoints. Information regarding pharmaogenetic (PGx) research is included in Appendix 4.

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 and date of birth will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of the study is to investigate the safety and tolerability of GSK2982772 following 12 weeks of treatment. No formal statistical hypotheses will be conducted to assess this objective.

If appropriate, comparisons between the GSK2982772 and the placebo arm will be made to investigate the secondary pharmacodynamic, mechanistic and efficacy objectives.

Trends over time will be investigated for both treatment arms along with associations between each of the pharmacodynamic, mechanistic and efficacy parameters.

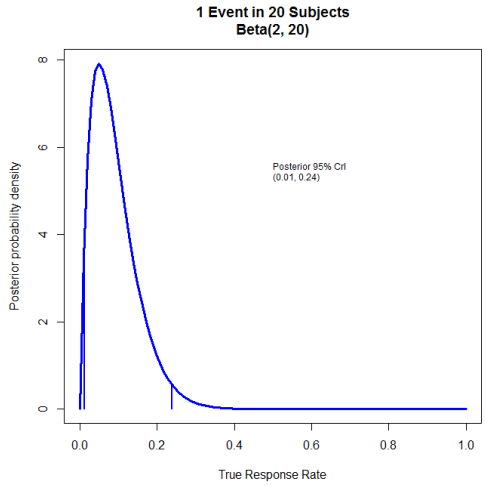
9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The study is not powered to detect pre-defined differences. A sufficient number of subjects will be screened so that approximately 30 subjects with moderate to severe RA are randomised into the study. Should the drop-out rate be higher than anticipated, additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor.

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772. Using a Bayesian approach to determine the confidence interval (CI) around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 20 then the posterior distribution would be Beta (2, 20), as outlined below in Figure 4.

Figure 4 One Event in 20 Subjects: Beta (2,20) Distribution



Thus, we can be 95% certain that the true probability of the safety event lies between 0.01 and 0.24.

For supportive information, the properties of the key secondary endpoint DAS28 have been considered.

Based on the estimate of variability (SD=1 from historical data) it is estimated that the lower and upper bounds of the 95% CI for the change from baseline in DAS28-CRP score will be within approximately 0.694 and 0.462 of the point estimate of GSK2982772 (n=20) and placebo (n=10).

9.2.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is lower than 20 in the GSK2982772 group, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in Table 4.

Table 4 Sample Size Sensitivity

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% Credible Interval indicating that a true incidence rate of x% could not be ruled out
20	0	16.1%
20	1	23.8%
20	2	30.4%
18	0	17.6%
18	1	26.0%
18	2	33.1%
16	0	19.5%
16	1	28.7%
16	2	36.4%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be conducted.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All Subjects Population: The 'All Subjects Population' is defined as subjects who were screened for the study. This population is used for the summary of selected accountability data.

Safety Population: The 'Safety Population' is defined as subjects who receive at least one dose of study medication. This population is used for the summary of all data including demography, safety, efficacy and exploratory data but excluding PK data.

Pharmacokinetic Population: The 'PK Population' is defined as subjects in the 'Safety' population who received an active dose and for whom a GSK2982772 pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only. Any PKPD analysis will be conducted on the Safety population such that subjects receiving placebo can be included.

9.3.2. Interim Analysis

A formal interim analysis will be conducted during the study. Additionally two review teams will monitor data on an ongoing basis for routine pharmacovigilance and decision making regarding the subsequent clinical development of GSK2982772 for RA.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT) which will include members of the GSK2982772 project team, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee, consisting of the GSK study physician, the study statistician, the study pharmacokineticist, the EDL and SRT Leader or designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data. The primary purpose of these informal reviews will be to monitor DAS28-CRP for futility. On review of DAS28-CRP data, the review group may recommend an interim analysis of key clinical and mechanistic data is first conducted prior to any decision to terminate the study for futility. A data review charter will identify the specific GSK individuals involved, outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted during the study. The timing of this analysis will either be on the recommendation of the data review group to assess futility based on 6 weeks of treatment, or when an appropriate number have completed 12 weeks of treatment, whichever is earliest. The purpose of the Interim Analysis would be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

All safety evaluations will be based on the Safety population. Clinical interpretation will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead ECG monitoring.

9.4.2. Secondary Analyses

The relationship between each of the mechanistic endpoints and also with the clinical endpoints will be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g., DAS28-CRP score). This may be conducted through comparing statistical models incorporating different explanatory terms (i.e. mechanistic endpoints) with the 'null' model (no mechanistic endpoints); or if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed.

Each endpoint will be considered individually and at the treatment level, where comparisons between treatment groups would be made on any changes observed, if deemed appropriate. This could include change from baseline in DAS28-CRP, which will be statistically analysed using a MMRM analysis comparing GSK2982772 with placebo at each time point. Additionally this could include, the proportion of subjects achieving ACR20/50/70 and DAS28-CRP response, which will be statistically analysed using a a Generalised Estimating Equation (GEE) model comparing GSK2982772 with placebo at each timepoint. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

9.4.3. Other Analyses

In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain change in DAS28 (i.e., comparator rate), based on the data that we have observed in the study.

GSK2982772 plasma concentrations will be summarised descriptively by day and nominal sampling time.

Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

9.4.3.1. Exploratory Analyses

All exploratory endpoints will be descriptively summarized, graphically presented and listed appropriately. Further details can be found 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

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) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the Investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

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

10.6. Records Retention

- Following closure of the study, the Investigator or the head of the medical institution (where applicable) must maintain all site study records (except for

those required by local regulations to be maintained elsewhere), in a safe and secure location.

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

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

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

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

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

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMD	Age-related macular degeneration
Anti-dsDNA	Anti-double stranded deoxyribose nucleic acid
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BID	Twice a day
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-Reactive Protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CYP	Cytochrome P
DAS	Disease Activity Score
DAS28	Disease activity score for 28 different joints
DAS28(CRP)	Disease activity score for 28 different joints with CRP value
DCE	Dynamic contrast enhanced
DNA	Deoxyribose Nucleic Acid
DMARD	Disease-Modifying Antirheumatic Drugs
DRC	Data Review Committee
ECG	Electrocardiogram
EDL	Early Development Lead
EMA	European Medicines Agency
ETCO2	End-tidal Carbon Dioxide
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTiH	First Time in Human
GCP	Good Clinical Practice
Gd	Gadolinium
GEE	Generalised Estimating Equations
GFR	Glomerular Filtrate Rate

GSK	GlaxoSmithKline
HAQ-DI	Disability Index of the Healthy Assessment Questionnaire
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
IRE	Initial rate of enhancement
IRTS	Interactive Response Technology System
Kg	Kilogram
L	Litre
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
ME	Maximal signal intensity enhancement
MedDRA	Medical Dictionary for Regulatory Activity
mg	Milligram
mL	Millilitre
MLKL	Mixed lineage kinase domain-like protein
mm	Millimeter
mmol	Millimole
MMP	Matrix metallopproteinase
MMRM	Mixed-effect Model Repeat Measurements
MRI	Magnetic Resonance Imaging
msec	millisecond
MRP	Myeloid-related Protein
MSDS	Material Safety Data Sheet
MTX	Methotrexate
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NOAEL	No Adverse Effect Level
NONMEM	Non Linear Mixed Effect Model
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NSF	Nephrogenic Systemic Fibrosis
OMERACT	Outcome Measures in Rheumatology
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PGA	Physician’s Global Assessment of Disease

PGx	Pharmacogenetics
PK	Pharmacokinetic
PPD	Tuberculin Purified Protein Derivative
PRO	Patient Reported Outcome
PSRAE	Possible Suicidality Related Adverse Event
PtGA	Patient Global Assessment of Disease
PTS IVIVT	Platform Technologies and Science In vivo In vitro Technology
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
R&D	Research and Development
RAP	Reporting and Analysis Plan
RAMRIQ	Rheumatoid arthritis MRI quantitative
RAMRIS	Rheumatoid arthritis MRI scoring system
RBC	Red Blood Cell
RF	Rheumatoid factor
RIP1	Receptor-interacting protein-1
RIP3	Receptor-interacting protein-3
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SIB	Suicidal Ideation Behaviour
SOP	Standard Operating Procedure
SpO2	Peripheral Capillary Oxygen Saturation
SRM	Study Reference Manual
SRT	Safety Review Team
TB	Tuberculosis
TEAR	Target Engagement Assay RIP1
TIMP	Tissue inhibitor of metalloproteinases
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TTS	Technical Terms of Supply
UK	United Kingdom
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor

Trademark Information

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12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>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, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study</td><td>• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 2 days after last dose[5]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications</td></tr>
</table>

treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<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]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

12.3. Appendix 3: Prednisolone Equivalent Dose Table

Drug Name	**Dose Equivalent to 1 mg Oral Prednisone**
Cortisone acetate	5 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg
Dexamethasone	0.15 mg

12.4. Appendix 4- 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 GSK2982772 or any concomitant medicines;
- Rheumatoid arthritis susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK2982772 has been completed and the study data reviewed. In some cases, the samples may not be studied.

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 and Baseline Failures

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

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

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

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

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

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

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

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the

Investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.5.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct

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

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias

- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.5.4. 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 PRO questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the PRO 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.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

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

12.5.6. 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 Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The Investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.6.1. 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 sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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

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 90 days after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
   - Contraceptive subdermal implant
   - Intrauterine device or intrauterine system

- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]

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

12.6.2. 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 fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to GSK as described in Appendix 4 While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will discontinue study medication or 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 and up to 90 days after the last dose of study medication. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.

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