# TITLE PAGE

**Division:** Worldwide Development
**Information Type:** Protocol Amendment

| | |
|---|---|
| **Title:** | A multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study with open label extension to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with active ulcerative colitis. |

**Compound Number:** GSK2982772

**Development Phase:** II

**Effective Date:** 20-APR-2017

**Protocol Amendment Number:** 01

**Author (s):** PPD [redacted]

**Revision Chronology**

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| Change in dosing regimen from 60 mg BID to 60 mg TID, updates to Inclusion criteria 3 and 6 and Exclusion criteria 3, 9, 21 and 22, allowance for rescreening, and addition of suicidality stopping criteria plus some minor protocol clarifications and administrative changes. | | |

2019N425893_00

2015N251758_01 **CONFIDENTIAL**

202152

**SPONSOR SIGNATORY**

PPD

20th April 2017

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202152

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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): IND 129,766; EudraCT 2016-001833-29

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202152

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 202152

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 202152

## Rationale

This study is the first experience with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with active ulcerative colitis (UC).

The primary objective of this study has not changed with amendment 01; however the dosing regimen does change to GSK2982772 (60 mg three times daily for both Parts A and B).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 60 mg or placebo three times daily for 42 days (Part A) followed by open label with GSK298772 60 mg three times daily for 42 days (Part B). In addition to 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 UC. 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 UC, 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 active ulcerative colitis. | • Adverse events.<br>• Clinical laboratory values (clinical chemistry, haematology and urinalysis).<br>• Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature).<br>• 12-Lead ECG monitoring. |
| **Secondary** | |
| • To investigate the preliminary efficacy of 60 mg three times daily doses of GSK2982772 in achieving mucosal healing after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • The proportion of subjects who achieve an absolute Mayo endoscopy subscore of 0 or 1 at Days 43 (Week 6) and 85 (Week 12).<br>• Change from baseline in mucosal appearance determined by Ulcerative Colitis Endoscopic Index of Severity (UCEIS). |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on biomarkers of disease activity in subjects with active ulcerative colitis. | • Change from baseline in markers which may include, but are not limited to, mean CRP and faecal calprotectin (FCP). |
| • To investigate the effect of 60 mg three | • Change from baseline in histologic |

| Objectives | Endpoints |
|---|---|
| times daily doses of GSK2982772 on histologic disease activity in subjects with active ulcerative colitis. | severity, including but not limited to Modified Riley Score and Geboes Index. |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 in achieving clinical response and remission after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • The proportion of subjects who achieve clinical response defined as reduction by ≥3 points or ≥30% improvement from baseline complete Mayo score, along with a decrease in the rectal bleeding score of ≥1 point, at Days 43 (Week 6) and 85 (Week 12).<br>• The proportion of subjects who achieve clinical remission defined as a complete Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, at Days 43 (Week 6) and 85 (Week 12). |
| • To investigate the preliminary efficacy of 60 mg three times daily doses of GSK2982772 in achieving symptomatic clinical remission after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • Change from baseline in partial Mayo score. |
| • To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily in subjects with active ulcerative colitis. | • Pre-dose plasma concentrations of GSK2982772 at Day 43 (Week 6).<br>• Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours.<br>• Trough concentrations on Day 85 (Week 12). |
| **Exploratory** | |
| • To investigate the effect of 60 mg three times daily doses of GSK2982722 on expression of inflammatory biomarkers in mucosal tissue biopsies in subjects with active ulcerative colitis. | • Change from baseline in inflammatory markers which may include, but are not limited to IL-1, IL-6, IL-8, MMP3, TNFα, IFNγ. |
| • To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and colon biopsy tissue. | • 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:<br>○ Target Engagement Assay RIP1 (TEAR1) in blood and colon |

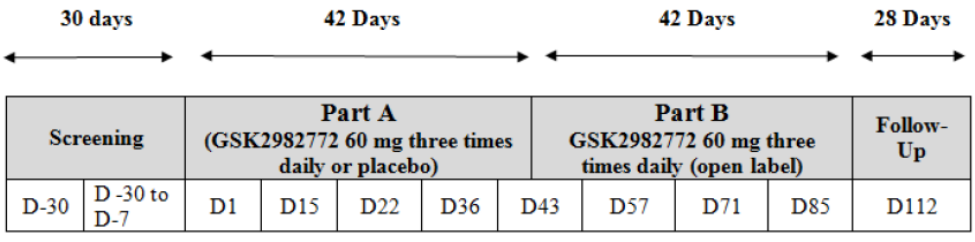
| Objectives | Endpoints |
|---|---|
| | tissue.<br>○ Phosphorylated or total RIP1, MLKL, RIP3, cleaved and total caspase 3 and caspase 8 signatures in colon tissue. |
| • To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the colon tissue after 60 mg three times daily doses of GSK2982772. | • Pre-dose GSK2982772 and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, in colon biopsies at Days 43 (Week 6) and 85 (Week 12), as evaluable samples and data permit. |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on quality of life in subjects with active ulcerative colitis. | • Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ). |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood subjects with active ulcerative colitis. | • Transcriptomic analysis of mRNA isolated from blood 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 colon tissue biopsies in subjects with active ulcerative colitis. | • Transcriptomic analysis of mRNA isolated from colon tissue biopsies at Screening, and Days 43 (Week 6) and trough on Day 85 (Week 12). |

## Overall Design

This is a multicentre, randomized, double-blind (sponsor-unblinded), placebo-controlled (Part A) study with an open label extension (Part B) to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with active UC. The study design schematic is depicted in Figure 1 below.

**Figure 1 Study Overview**

Amendment 01:



Prior to amendment 01:


| Screening | | Part A GSK2982772 60 mg twice daily or placebo | | | | Part B GSK2982772 60 mg twice daily (open label) | | | | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|
| D-30 | D -30 to D-7 | D1 | D15 | D22 | D36 | D43 | D57 | D71 | D85 | D112 |

**Key assessments:**
Safety assessments, PK samples, Mayo score, Modified Riley Score, Geboes Index, IBDQ, PD samples

## Treatment Arms and Duration

Each subject will participate in the study for approximately 20 weeks. This includes a screening period 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 2-part treatment period (Part A and Part B) and start treatment (or dosing) on Day 1.

The Follow-up Period is 28 days (4 weeks) long.

Part A: Approximately 36 subjects who have completed screening assessments and are eligible will be randomized in a 2:1 ratio (active to placebo) to one of the following study treatments for 42 days:

GSK2982772 60 mg three times daily (TID)

Placebo three times daily (TID)

Part B: Is a 6 week open label extension where **all** subjects who have completed Part A will receive 60 mg GSK2982772 three times daily (TID) for 42 days.

Prior to amendment 01 being effective in each country, subjects have been randomised in a 2:1 ratio (active to placebo) to one of the following treatments for Part A:

GSK2982772 60 mg two times daily (BID) x 42 days

Placebo two times daily (BID) x 42 days

Part B: A 6 week open label extension where **all** subjects who have completed Part A received 60 mg GSK2982772 two times daily (BID) for 42 days.

## Type and Number of Subjects

A sufficient number of subjects will be screened so that approximately 30-36 subjects with active UC will be randomised into the study on a TID regimen. Prior to protocol amendment 01 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Should the dropout rate in Part A [Day 1 through 43 (Week 6)] be higher than anticipated, or the sample size review warrants an increase in randomised subjects, additional or replacement subjects may be randomised (up to an overall total maximum of 60) into the study at the discretion of the Sponsor. Subjects who discontinue participation during the open label phase in Part B [(Day 43 (Week 6) through Day 85 (Week 12)] will not be replaced.

## Analysis

The safety and tolerability of GSK2982772 following 6 and 12 weeks of treatment will be based on summaries of adverse events, clinical laboratory values, vital sign measurements and 12-lead ECG monitoring.

Two interim analyses are planned. The first Interim Analysis will be conducted on the recommendation of the Data Review Committee to assess futility based on 6 weeks of treatment, or when an appropriate number have completed 6 weeks of treatment, whichever is earliest. The purpose of the Interim Analysis would be to assess whether to stop the study for futility and, if appropriate, to perform a sample size re-estimation. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for UC.

Interim Analysis #2 will occur when an appropriate number have completed 12 weeks of treatment. The purpose of the Interim Analysis 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 UC.

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 is to monitor mucosal healing rates and any available target engagement and inflammatory biomarker data for internal decision making.

A data review charter will outline in detail the activities of the informal reviews and the interim analyses, futility criteria, and how the integrity of the study will be maintained.

Safety data collected in Part A and Part B of the study will be combined and summarised according to treatment received for the first six weeks of treatment and overall. Efficacy, PD and biomarker data will be summarised for Part A, and supporting summaries and analyses, as appropriate, will be summarised for Part A and Part B combined according to treatment received.

Comparisons between treatment groups in Part A on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement and changes in inflammatory markers will be statistically analyzed using a Mixed-effect Model Repeat Measurements (MMRM) comparing GSK2982772 with placebo at each time point. The proportion of subjects achieving Mayo Endoscopy Remission (Scores of 0 or 1), will be statistically analysed using a Generalise Estimating Equations (GEE) model comparing GSK2982772 with placebo at each time point if appropriate. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

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., Mayo Endoscopy Scores). 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.

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 proportion of Mayo Endoscopic Remission (0 or 1) (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 active ulcerative colitis (UC) who are currently being treated with standard of care therapy. All subjects will be allowed to continue standard of care therapy 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 01; however the dosing regimen does change to GSK2982772 (60 mg three times daily for both Parts A and B).

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg three times daily for 43 and 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 active UC.

## 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 TNF family cytokines, ligands for TLR3/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.

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) characterized by chronic relapsing and remitting inflammation of the colon. Histologically, there is evidence for both necrosis and apoptosis in biopsies from UC subjects [Dourmashkin, 1983; Vitali, 2011], [Seidelin, 2013; Regeling, 2016; Seidelin, 2015; Sipos, 2005]. Interestingly, inhibition of RIPK1 blocks spontaneous cytokine release in biopsies from UC patients in ex vivo culture models [GlaxoSmithKline Document Number 2014N204126_02]. In addition to human translational data in IBD, bolus administration of TNF to mice results in a severe intestinal inflammation that is entirely RIPK1-dependent [Duprez, 2011; GlaxoSmithKline Document Number 2014N204126_02], and murine models that genetically skew TNF signaling down the RIPK1 pathway in the gut results in spontaneous ileal and colonic inflammation [Günther, 2011; Welz, 2011]. Overall, these data build a compelling case for the role of RIPK1 in IBD pathogenesis.

While the pathobiology of UC is complex, the introduction of anti-TNF biologics has improved the treatment landscape for UC patients with moderate to severe disease. Additional emerging therapies include biologics which interfere with gut-specific lymphocyte trafficking. However, all biologics may have limitations with regard to long-term efficacy, development of anti-drug antibodies, and side effect profiles. There remains a high unmet need for novel treatments which will not only reduce signs and symptoms, but will maintain mucosal healing and achieve long term remission.

## 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 ulcerative colitis. | • Adverse events.<br>• Clinical laboratory values (clinical chemistry, haematology and urinalysis).<br>• Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature).<br>• 12-Lead ECG monitoring. |
| **Secondary** | |
| • To investigate the preliminary efficacy of 60 mg three times daily doses of GSK2982772 in achieving mucosal healing after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • The proportion of subjects who achieve an absolute Mayo endoscopy subscore of 0 or 1 at Days 43 (Week 6) and 85 (Week 12).<br>• Change from baseline in mucosal appearance determined by Ulcerative Colitis Endoscopic Index of Severity (UCEIS). |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on biomarkers of disease activity in subjects with active ulcerative colitis. | • Change from baseline in markers which may include, but are not limited to, mean CRP and faecal calprotectin (FCP). |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on histologic disease activity in subjects with active ulcerative colitis. | • Change from baseline in histologic severity, including but not limited to Modified Riley Score and Geboes Index. |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 in achieving clinical response and remission after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • The proportion of subjects who achieve clinical response defined as reduction by ≥3 points or ≥30% improvement from baseline complete Mayo score, along with a decrease in the rectal bleeding score of ≥1 point, at Days 43 (Week 6) and 85 (Week 12).<br>• The proportion of subjects who achieve clinical remission defined as a complete Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, at Days 43 (Week 6) and 85 (Week 12). |
| • To investigate the preliminary efficacy of 60 mg three times daily doses of GSK2982772 in achieving symptomatic clinical remission after 6 and 12 weeks of | • Change from baseline in partial Mayo score. |

| Objectives | Endpoints |
|---|---|
| treatment in subjects with active ulcerative colitis. | |
| • To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily in subjects with active ulcerative colitis. | • Pre-dose plasma concentrations of GSK2982772 at Day 43 (Week 6).<br>• Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours.<br>• Trough concentrations on Day 85 (Week 12). |
| **Exploratory** | |
| • To investigate the effect of 60 mg three times daily doses of GSK2982722 on expression of inflammatory biomarkers in mucosal tissue biopsies in subjects with active ulcerative colitis. | • Change from baseline in inflammatory markers which may include, but are not limited to IL-1, IL-6, IL-8, MMP3, TNFα, IFNγ. |
| • To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and colon biopsy tissue. | • 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:<br>○ Target Engagement Assay RiP1 (TEAR1) in blood and colon tissue.<br>○ Phosphorylated or total RIP1, MLKL, RIP3, cleaved and total caspase 3 and 8 signatures in colon 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 colon tissue after 60 mg three times daily doses of GSK2982772. | • Pre-dose GSK2982772 and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, in colon biopsies at Days 43 (Week 6) and 85 (Week 12), as evaluable samples and data permit. |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on quality of life in subjects with active ulcerative colitis. | • Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ). |
| • To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood subjects with active ulcerative colitis. | • Transcriptomic analysis of mRNA isolated from blood 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 colon tissue biopsies in subjects with active ulcerative colitis. | • Transcriptomic analysis of mRNA isolated from colon tissue biopsies at Screening, and Days 43 (Week 6) and trough on Day 85 (Week 12). |

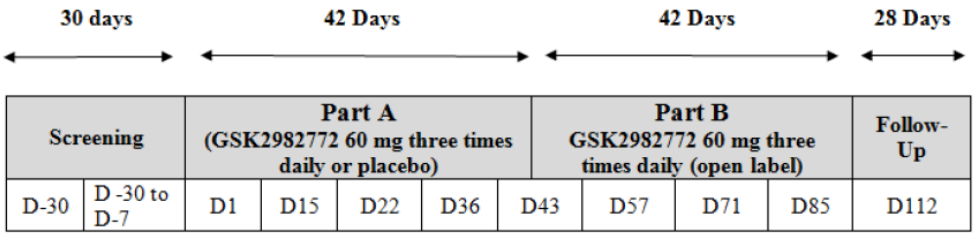
# 4. STUDY DESIGN

## 4.1. Overall Design

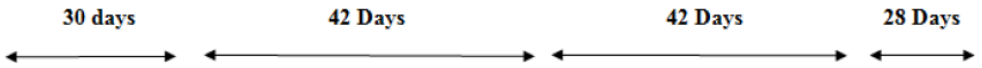
This is a multicentre, randomized, double-blind (sponsor-unblinded), placebo-controlled study with an open label extension to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with active UC. The study design schematic is depicted in Figure 2 below.

**Figure 2 Study Overview**

Amendment 01:



Prior to amendment 01:




| Screening | | Part A GSK2982772 60 mg twice daily or placebo | | | | Part B GSK2982772 60 mg twice daily (open label) | | | | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|
| D-30 | D -30 to D-7 | D1 | D15 | D22 | D36 | D43 | D57 | D71 | D85 | D112 |

**Key assessments:**
Safety assessments, PK samples, Mayo score, Modified Riley Score, Geboes Index, IBDQ, 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 will enter the 2-part treatment period (Part A and Part B) 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 42 days (6 weeks) in a 2:1 ratio in Part A. All subjects will move to open label in Part B to receive GSK2982772 60 mg three times daily (approximately 8 hours apart) for an additional 42 days (6 weeks). Treatment duration is a total of 84 days (12 weeks) inclusive of Parts A and B. Subjects that were randomised prior to protocol amendment 01 being approved in each country were randomly assigned to either GSK2982772 60 mg or placebo orally two times daily (approximately 12 hours apart) for 42 days followed by GSK2982772 60 mg BID for 42 days.

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, 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 8, 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 which will they will be instructed to record their daily study medication and concomitant medication administration and any adverse events.

### 4.2.3. Follow-up Period

After the open label (Part B) Treatment Period, the subject will enter the Follow-up Period which lasts for 28 days post the last administration of study medication, in order 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 - 36 subjects with active UC will be randomised into the study on a TID regimen. Prior to protocol amendment 01 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen. Should the dropout rate in Part A [Day 1 through 43 (Week 6)] be higher than anticipated, or the sample size review warrant an increase in subject numbers, additional or replacement subjects may be randomised (up to an overall total maximum of 60) into the study at the discretion of the Sponsor. Subjects who discontinue participation during the open label phase in Part B [(Day 43 (Week 6) through Day 85 (Week 12)] will not be replaced.

## 4.4. Design Justification

As this is the first trial of GSK2982772 in subjects with UC, 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, along with preliminary efficacy in achieving mucosal healing, to understand whether GSK2982772 is inhibiting the pathway of interest in this disease.

Because mucosal healing has been increasingly recognized as a key endpoint in UC randomised controlled trials (RCTs), sigmoidoscopy will be performed at baseline (screening) and at the Day 43 (Week 6) and Day 85 (Week12) time points. The mid-point Day 43 (Week 6) endoscopic assessment was chosen based on evidence that improvement in mucosal inflammation may be achievable as early as 4 weeks after initiation of anti-TNF therapy [Fratila, 2010] and 6 weeks with anti-integrin therapy [Feagan, 2013]. This suggests endoscopic evidence of disease improvement may be more sensitive in measuring therapeutic efficacy than traditional disease activity index scores in shorter duration trials. The 85 day (12 week) duration of treatment is based on review of previous proof of mechanism and proof of concept studies in UC [Reinisch, 2011; Sandborn, 2012; Sandborn, 2014] and is limited by the supporting 13 week toxicology studies.

It is expected that an effective therapy should cause trends in group level changes in the mechanistic parameters by both the Day 43 (Week 6) and Day 85 (Week 12) time points. The placebo group was deemed necessary as primary objective is safety, and ideally this would be reviewed in a placebo controlled blinded trial. However, the size of the placebo group has been kept to a minimum and is limited to Part A [Day 1 through 43 (Week 6)]. Part B [Day 43 (Week 6) through Day 85(Week12)] was designed as an open label extension study to aid recruitment and retention as well as to obtain additional safety, PK and biomarker data in this study. All subjects will be allowed to continue standard of care therapy during the study (with the exception of biologics), 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 from the single dose ascending part of study 200975, a 60 mg BID dose was predicted to have on average 95% RIP1 target engagement and approximately 90% of subjects will have >90% target engagement 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 is currently available about the distribution of GSK2892772 into gastrointestinal (GI) tissue.

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 $1/5^{th}$ 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. No subjects have been randomised yet to this study (Study 202152).

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 Investigator's Brochure [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**:<br>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.<br><br>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.<br><br>**Clinical data**:<br>A First Time in Human (FTiH) study with single ascending and multiple ascending doses has been performed in 67 healthy male volunteers to date. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02]. No drug-associated CNS adverse events were identified and no Serious Adverse Effects (SAEs) were reported. | **Subject Selction**:<br>• Subjects with known history of significant progressive neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded.<br>• Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening.<br><br>**Subject Monitoring**:<br>• 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**:<br>• Subjects with recurrent, chronic or active infections will be excluded from the study.<br>• 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**:<br>In the FTiH study, no SAEs were reported. One subject experienced an AE herpes zoster approximately 42 days after receiving his last dose with GSK2982772. The blinded Investigator determined this to be potentially drug-related. | **Subject Monitoring**:<br>• Subjects will be monitored for signs of infection.<br>• 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**:<br>• 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.<br>• 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).<br>• Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in subjects with UC. |
| Respiratory | **Non-clinical data**:<br>In the single-dose Safety Cardiovascular 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.<br><br>In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (minute volume) or respiratory rate were | **Subject Monitoring**:<br>• Subjects should be monitored for standard respiratory-related adverse events.<br>• Vital signs will be monitored during study visits. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02].<br><br>**Clinical data**:<br>In the FTiH study, repeat doses of GSK2982772 up to 60 mg BID 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.<br><br>**Clinical data**:<br>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**:<br>• 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.<br>**Subject Monitoring:**<br>• Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour.<br>• 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**:<br>In an early rat embryofetal development study, there was no maternal or developmental toxicity at doses ≤200 mg/kg/day.<br>In an early 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 | **Subject Selection**:<br>• 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 |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | developmental toxicity was evident at doses up to 300 mg/kg/day. | study drug (Appendix 6).<br>• Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study.<br>• Pregnant and lactating females are not eligible for inclusion in the study.<br>**Withdrawal criteria**:<br>• 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**:<br>In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (Pgp) inhibitors were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772.<br><br>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.<br><br>GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772.<br><br>See Section 4.3.6 of GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. | **Subject Selections**:<br>• 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.<br><br>**Subject Monitoring:**<br>• Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study.<br>• Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Procedures** | | |
| Sigmoidoscopy with biopsy | Potential risks of the procedure include discomfort, perforation or bleeding. | **Subject Management**:<br>• Sigmoidoscopy, rather than colonoscopy will be used which is thought to reduce the risk of endoscopy related complications by up to 50%.<br>• Sigmoidoscopy will be performed by experienced and trained staff only.<br>• Subjects will be instructed about amount of expected bleeding post-procedure and will be instructed to contact the clinical site should there be any adverse clinical events after the procedure. |

### 4.6.2. Benefit Assessment

There are additional treatment options available for subjects who have an inadequate response to current therapies for UC. It is possible that treatment with GSK2982772 may be effective in the treatment of UC, 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 acceptable based on limited direct benefits that may be afforded to patients with active UC by contributing to the understanding of the disease and the development of new therapies for patients with UC 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 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 UC.

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 active UC, 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 active UC, as documented by complete diagnostic colonoscopy to the terminal ileum (TI) with biopsy performed ≥ 3 months prior to screening. If diagnostic colonoscopy was not performed to the TI, it must be documented by the PI that the subject has diffuse inflammation from the rectum extending proximally to the colon in a continuous and uniform way.
4. A Complete Mayo Score of ≥3 points and endoscopy sub score of 2 to 3 at screening, despite concurrent treatment with **at least 1** of the following (oral corticosteroids or any oral 5-aminosalicylates (5-ASA) or purine analogues or all as defined below):
    a. Oral 5-ASA at a stable dose (equivalent to ≥ 2.4 g/day of Asacol) for at least 4 weeks prior to first dose. Must remain on a stable dose until end of treatment.
    b. Purine analogues (azathioprine, mercaptopurine, thiopurines) or methotrexate for at least12 weeks prior to first dose. Must remain on a stable dose until end of treatment.
    c. Stable low dose oral corticosteroid (up to 20 mg prednisolone or equivalent) for 2 weeks prior to sigmoidoscopy. Must remain on a stable dose until end of treatment.
5. If on rectal 5-ASA or corticosteroids, must remain on a stable dose for at least 4 weeks prior to first dose. Must remain on stable dose until the end of treatment.
6. Subject is naive to any biological therapies for UC.
   **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) prior to first dose.
   **OR**
   Subject may have had previous exposure to a single biologic agent (e.g., vedolizumab) in the context of a previous clinical trial. The biologic agent must have been discontinued more than 8 weeks (or 5 half lives whichever is longer) prior to first dose.
   **Note: Exposure to a single biologic agent is not required in addition to Inclusion #4 and #5 above.**

| WEIGHT |
|---|
| 7. A body mass index (BMI) within range of 18.5 – 35 kg/m2 (inclusive) at screening. |

| SEX |
|---|
| 8. Male and female subjects:<br><br>**Males:**<br><br>Male subjects with female partners of child bearing potential must comply with the following contraception requirements in Appendix 6.<br><br>**Females**:<br><br>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:<br><br>a. Non-reproductive potential defined as:<br>• Pre-menopausal females with one of the following:<br>• Documented tubal ligation<br>• Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion<br>• Hysterectomy<br>• Documented Bilateral Oophorectomy<br>• 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.<br><br>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 2 days after the last dose of study medication and completion of the follow-up visit.<br><br>The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. |

| INFORMED CONSENT |
|---|
| 9. 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 diagnosis of indeterminate colitis, Crohn's Disease, infectious colitis, or ischemic colitis. |
| 2. Subject with fulminant UC, or UC limited to the rectum (disease extent <15 cm from the anal verge). |
| 3. Subject with previous small bowel or colonic surgery (with exception of appendectomy), histological evidence of colonic dysplasia or bowel stricture. |
| 4. Subject with colostomy, fistulae or known symptomatic stenosis of the intestine. |
| 5. Subject with toxic megacolon. |
| 6. Subject with positive Clostridium difficile toxin test or active/previous colonic CMV infection. |
| 7. Subject with current history of suicidal ideation behaviour (SIB) as measures using the Columbia Suicide Severity Rating Scale (C-SSRS) or history of attempted suicide. |
| 8. An active infection, or a history of infections as follows:<br>• Hospitalisation for treatment of infection within 60 days before first dose (Day 1).<br>• Currently on any suppressive therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).<br>• Use of parenteral (IV or intramuscular) antibiotics (antibacterials, antivirals, antifungals, or antiparasitic agents) for an infection within 60 days before first dose.<br>• A history of opportunistic infections within 1 year of screening (e.g. pneumocystis jirovecii, CMV pnemonitis, 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.<br>• 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.<br>• History of TB, irrespective of treatment status.<br>• 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 follow-up chest x-ray, locally read by a radiologist, 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.

9. 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 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).
10. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
11. Current active or chronic history of liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones).
12. 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.
13. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency unless subject has a documented history of selective IgA deficiency.
14. A major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
15. Any planned surgical procedure during the study.
16. 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.

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 GSK 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. 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 (not inclusive of any UC registry study where no study medication is being administered) at the same time as participating in this clinical trial. |

| DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA |
|---|
| 22. Haemoglobin <10 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. |
| 23. 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. |
| 24. A positive serology for human immunodeficiency virus (HIV) 1 or 2 at screening. |
| 25. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months. |
| 26. 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 (SAEs). 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 (preferably before performing sigmoidoscopy), 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 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 medication for the treatment of UC 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

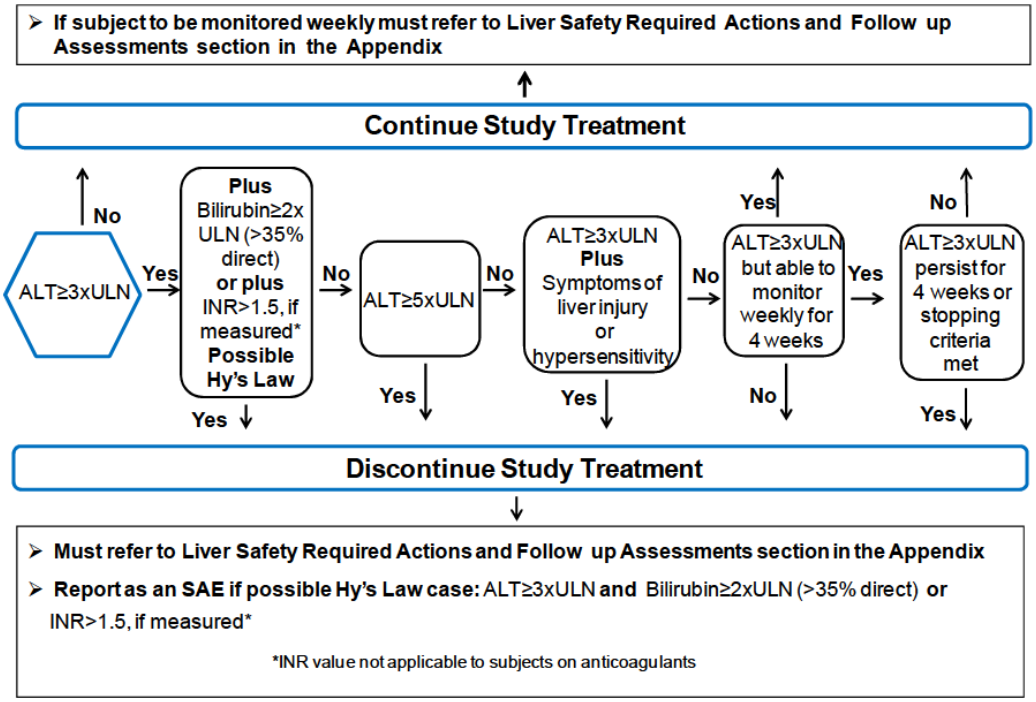
In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subject will be regularly reviewed by the Sponsor Safety Review Team (SRT) in order to ensure appropriate subject safety. Any changes to the study 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 or an absolute decrease of ≥ 3 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 01):** | 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 01):** | 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.

In Part A, subjects will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio for 42 days. In Part B, all subjects who have completed Part A will then receive GSK2982772 in open label for 42 days.

## 6.3. Planned Dose Adjustments

No dose adjustments are allowed.

## 6.4. Blinding

This will be 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 Leader (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 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 by a member of the study site staff.

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 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.
- Subject will abstain from strenuous exercise for 24 hours after sigmoid biopsy procedures.

## 6.11. Concomitant Medications and Non-Drug Therapies

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

Medications for the treatment of UC 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 |
|---|---|
| 5-ASA (≥ 2.4 g/day) | Stable dose regimen for at least 4 weeks prior to first dose (Day 1) and throughout the study. |
| Purine analogues (azathrioprine, mercaptopurine, thiopurines) | Stable dose regimen for at least12 weeks prior to first dose (Day 1) and throughout the study. |
| Methotrexate (MTX) | Stable dose regimen for at least 12 weeks from first dose (Day 1) and throughout the study. |

| Drug | Requirement |
|---|---|
| Oral corticosteroids (up to 20 mg prednisolone or equivalent). See Appendix 3 for equivalent doses. | Stable dose regimen for at least 2 weeks prior to sigmoidoscopy and throughout the study. |
| Topical (rectal) corticosteroids or 5-ASA | Stable dose regimen for at least 4 weeks prior to first dose (Day 1) and throughout the study. |

### 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 UC 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 GSK medical monitor.

**Table 2 Prohibited Medications**

| Therapy | Time period |
|---|---|
| A change in dose of 5-ASA | 4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112) |
| A change in dose of purine analogue | 12 weeks prior to first dose (Day 1) until after the follow up visit (Day 112) |
| A change in dose of MTX | 12 weeks prior to first dose (Day 1) until after the follow up visit (Day 112). |
| Greater than 20mg/day oral prednisolone (or equivalent corticosteroid) or a change in dose of corticosteroid. | 2 weeks prior to sigmoidoscopy until after the follow up visit (Day 112). |
| A change in dose or frequency of topical (rectal) corticosteroids or topical (rectal) 5-ASA. | 4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112). |
| Exposure to more than one anti-TNF biologic therapy including but not limited to anti-TNF biologics, infliximab, adalimumab, and golimumab.<br><br>**Exception**: Exposure to a single anti-TNF-biologic for which the subject the subject discontinued for a reason other than primary non-response. | Cannot have been exposed to more than 1 anti-TNF biologic or be on biologic therapy at any time during the study.<br><br>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). |
| Exposure to a single biologic therapy for the treatment of UC (other than anti-TNF as detailed above), including but not limited to | Cannot have been on at any time, except for vedolizumab in a clinical trial setting where it must have been discontinued for 8 weeks or 5 |

| Therapy | Time period |
|---|---|
| vedolizumab.<br>**Exception**: vedolizumab previously administered in a clinical trial setting. | half lives (whichever is longer) prior to first dose. |
| 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). |
| Live vaccination | Liver 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 influenza, in subjects with UC. |

# 7. STUDY ASSESSMENTS AND PROCEDURES

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

Supplementary study conduct information not mandated to be present in this protocol is provided in the Study Reference Manual (SRM) and laboratory manual. The SRM and laboratory manual 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 exact 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 other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- 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) | Screening (-7 to -30) | Treatment Period[18] | | | | | | | | | | | | | Early Withdrawal[19] | Follow Up (±3)[20] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PART A | | | | | | | PART B | | | | | | | |
| | | | 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 | | 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[4] | | X | | X | | X | X | X |
| 12-lead ECG[3] | X | | X[4] | | X | | X | | X[4] | | X | | X | | X | X | X |
| Concomitant medication review & AE reporting/SAEs[5] | | | X----------X | | | | | | | | | | | | | | |
| **PROs/Questionnaires/Disease Assessments and Procedures** | | | | | | | | | | | | | | | | | |
| Columbia Suicide Severity Rating Scale (C-SSRS) | X | | X[4] | | | | | | X[4] | | | | | | X | X | |
| IBDQ[6] | | | X[4] | | | | | | X[4] | | | | | | X | X | |
| UCEIS, Modified Riley, Geboes | X-------X[7] | | | | | | | | X[4] | | | | | | X | X | |

| Procedures | Screening (-30) | Screening (-7 to -30) | Treatment Period[18] | | | | | | | | | | | | | Early Withdrawal[19] | Follow Up (±3)[20] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PART A | | | | | | | PART B | | | | | | | |
| | | | 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) | | |
| Mayo Score (including sigmoidoscopy and biopsy) | X-----X[7] | | | | | | | | X[4, 8] | | | | | | X | X[9] | |
| Partial Mayo Score | X-----X[7] | | | | X | | X | | X[4] | | | | | | X | X | |
| **Study Treatment** | | | | | | | | | | | | | | | | | |
| Randomisation | | | X | | | | | | | | | | | | | | |
| Study medication (three times daily)[10] | | | X----------XX----------X[11] | | | | | | | | | | | | | | |
| Dispensing of study medication | | | X | | X | | | | X | | | | | | | | |
| Dispensing of diary cards | | | X | | X | | X | | X | | X | | X | | | | |
| Collection of diary cards | | | | | X | | X | | X | | X | | X | | X | | |
| **Laboratory (Safety) Assessments and Procedures** | | | | | | | | | | | | | | | | | |
| TB, HIV, Hep B, Hep C Ab, C. Difficile toxin | X | | | | | | | | | | | | | | | | |
| FSH & estradiol (if applicable) | X | | | | | | | | | | | | | | | | |
| Serum pregnancy test (WCBP only) | X | | | | | | | | | | | | | | | | |
| Urine pregnancy test (WCBP only)[12] | | | X[4] | | X | | X | | X[4] | | X | | X | | X | X | X |
| Haematology, chemistry, urinalysis | X | | X[4] | | X | | X[13] | | X[4] | | X[13] | | X[13] | | X | X | X |
| Faecal calprotectin[14] | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Blood sample for exploratory biomarkers and TE[15] | | | X[4] | | | | | | X[4] | | | | | | X | X | |

| Procedures | Screening (-30) | Screening (-7 to -30) | Treatment Period[18] | | | | | | | | | | | | | Early Withdrawal[19] | Follow Up (±3)[20] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PART A | | | | | | | PART B | | | | | | | |
| | | | 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) | | |
| PK blood samples GSK2982772[16] | | | X | | | | | | X[4] | | | | | | X | X | |
| Biopsies for PK, inflammatory biomarkers, mRNA, TE & pathway marker analysis | X-------X[7] | | | | | | | | X[4] | | | | | | X | X[8] | |
| Pharmacogenetic sample (PGx)[17] | | | X | | | | | | | | | | | | | | |

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. PRO assessments should be conducted before any tests, procedures or assessments to avoid influencing the subjects' perception.
7. Sigmoidoscopy may be performed at any time during the screening window as an additional visit (if required) up to Day -7 in order for central reading confirmation of Mayo Score for inclusion. If a shorter window is required (e.g., within Day -3 to Day -7), this will be permitted as long as it has been confirmed with the sponsor and central reader that results of the Mayo endoscopy score will be available before end of the screening window. Histological disease (e.g., UCEIS, MRS and Geboes Index) along with Mayo score assessments will also be completed.
8. Sigmoidoscopy may be performed on a separate day within the Day 43 visit window allowance (±3 days). A separate visit to perform sigmoidoscopy is only allowed to accommodate scheduling. This separate visit should be done before the full Day 43 visit where PK, clinical laboratory tests and all other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the sigmoidoscopy procedure and also the morning before the full Day 43 visit, if being done on a separate day. Dispensing of study medication must be done at the 2nd visit (if separate visits are performed).
9. Biopsy only required at Early Withdrawal visit if after at least 14 days of treatment and prior to Day 43 or if after Day 57 and prior to Day 85.

10. 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 43 and 85, subjects must not take their study medication at home in the morning. Subjects will complete specified pre-dose assessments and then will be administered their morning dose of medication at site on Day 43. On Day 85, subjects are no longer receiving study medication.
11. In Part A, subjects will be randomised 2:1 to GSK298722 60 mg or placebo three times daily for 42 days. At the Day 43 visit, all subjects who have completed Part A, will move in to Part B open label treatment with GSK2982772 60 mg three times daily for 42 days.
12. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
13. Urinalysis not required on Days 29, 57 and 71.
14. Subjects can provide a faecal sample at any time during the screening window and up to 48 hours prior to any visit where FCP is being collected. Please see laboratory manual for full details on sample handling and procedure.
15. Blood samples for exploratory biomarkers and Target engagement. See laboratory manual for full details on sample collection, handling and shipment.
16. PK blood samples for GSK2982772 will be taken pre-dose on Day 43. Post-dose serial PK samples will be taken on Days 1 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or Early Withdrawal.
17. A PGx blood sample is collected at the baseline visit (Day 1), after the subject has been randomized 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 randomization.
18. Visit windows during the treatment period are relative to Day 1.
19. 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.
20. Follow-up visit should be completed 28 days (±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 and smoking history (as detailed in the CRF) will be assessed at screening.

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

## 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 202152 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 (AE) 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 for 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 or 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 Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed 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 Count; Hemoglobin; Hematocrit<br>*RBC Indices:* MCV; MCH<br>*WBC count with Differential:* Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils |
| Clinical Chemistry [3] | BUN; Creatinine; Glucose[4]; CRP; LDL cholesterol[4]<br>Potassium; Sodium; Calcium; Triglycerides[4]<br>AST (SGOT); ALT (SGPT); Alkaline phosphatise; Total Cholesterol[4]<br>Total and direct bilirubin; Total Protein; Albumin; HDL cholesterol[4] |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood and ketones by dipstick<br>• Microscopic examination (if blood or protein is abnormal) |
| Other Screening and RoutineTests | • HIV 1 & 2<br>• Hepatitis B (HBsAg)<br>• Hepatitis B core antibody (HBcAb)<br>• Hepatitis C (Hep C antibody)<br>• QuantiFeron Gold Test<br>• T-spot (if QuantiFeron is indeterminant)<br>• FSH and estradiol (as needed in women of non-child bearing potential only)<br>• Urine hCG Pregnancy test (as needed for women of child bearing potential) [5]<br>• 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.<br>• Estimated glomerular filtrate rate (eGFR) will be calculated using the CKD-EPI formula.<br>• C. Difficile toxin. |

**Footnotes** :
1. The subject's CBC results from the previous scheduled visit may be checked prior to the sigmoidoscopy 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 UC. 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 GSK2982722 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. 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. Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a 32-item Inflammatory Bowel Disease-specific healthy related quality of life instrument evaluating general activities of daily living, intestinal function, social

performance, personal interactions, and emotional status. The IBDQ questionnaire will be completed by each subject as detailed in Section 7.1. Items responses are summed-up for a total score and also averaged among four dimensions: bowel function (10 items), systemic symptoms (5 items), social function (5 items), and emotional status (12 items).

### 7.4.2. Clinical Disease Assessments

Brief details are given below and detailed procedural instructions are given in the SRM.

#### 7.4.2.1. Mayo Score

The Mayo Score is a 12-point scoring system (Table 4) used to assess UC disease activity based on CCI and CCI.

A partial Mayo Score is a scoring system where disease activity is evaluated based on CCI and CCI, without endoscopic components.

Total and Partial Mayo Scores will be collected and scored centrally at all time points indicated in Section 7.1.

**Table 4 Mayo Score**

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

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

### 7.4.2.2. Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

UCEIS will be used as an additional tool to assess disease activity based on endoscopic CCI and CCI (Table 5). It has been shown to accurately predict overall assessment of endoscopic severity of UC [Travis, 2012]. The UCEIS is a scoring system UCEIS will be collected and scored centrally at all time points indicated in Section 7.1.

**Table 5 UCEIS**

| Descriptor (score most severe lesions) | Likert scale anchor points | Definitition |
|---|---|---|
| CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. | | |

| Descriptor (score most severe lesions) | Likert scale anchor points | Definitition |
|---|---|---|
| CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. | | |

### 7.4.3. Histological Disease Assessments

Biopsy samples taken during sigmoidoscopy will be scored centrally using both the Geboes Index [Geboes, 2000] and Modified Riley Score [Riley, 1991] which are histological scoring indices for evaluation of disease activity in UC.

Histology will be assessed at the time points indicated in Section 7.1.

#### 7.4.3.1. Geboes Index

The Geboes Index is shown in Table 6. Upon scoring of all components of the index, the highest grade with a subgrade above 0 will be recorded as a histological score.

**Table 6 Geboes Index**

| Grade | | Subgrade | |
|---|---|---|---|
| 0 | Structural (architectural change) | 0.0 | No abnormality |
| | | 0.1 | Mild abnormality |
| | | 0.2 | Mild or moderate diffuse or multifocal abnormalities |
| | | 0.3 | Severe diffuse or multifocal abnormalities |
| 1 | Chronic inflammatory infiltrate | 1.0 | No increase |
| | | 1.1 | Mild but unequivocal increase |
| | | 1.2 | Moderate increase |
| | | 1.3 | Marked increase |

| Grade | | Subgrade | |
|---|---|---|---|
| **2** | **Lamina propria eosinophils and neutrophils (to be graded separately)** | **2.0** | No increase |
| | | **2.1** | Mild but unequivocal increase |
| | | **2.2** | Moderate increase |
| | | **2.3** | Marked increase |
| **3** | **Neutrophils in epithelium** | **3.0** | None |
| | | **3.1** | <5% crypts involved |
| | | **3.2** | <50% crypts involved |
| | | **3.3** | >50% crypts involved |
| **4** | **Crypt destruction** | **4.0** | None |
| | | **4.1** | Probable – local excess of neutrophils in part of crypt |
| | | **4.2** | Probable – marked attenuation |
| | | **4.3** | Unequivocal crypt destruction |
| **5** | **Erosion or ulceration** | **5.0** | No erosion, ulceration, or granulation tissue |
| | | **5.1** | Recovering epithelium plus adjacent inflammation |
| | | **5.2** | Probable erosion – focally stripped |
| | | **5.3** | Unequivocal erosion |
| | | **5.4** | Ulcer or granulation tissue |

#### 7.4.3.2. Modified Riley Score (MRS)

The Modified Riley Score (MRS) shown in Table 7. This is a 4 point scale (none, mild, moderate and severe) which scores histologic activity based on localization and quantification of neutrophils in the mucosa.

**Table 7 Modified Riley Score**

| Activity | | Histological Characteristics |
|---|---|---|
| **None** | **0** | Neutrophils in epithelium = none |
| **Mild** | **1** | Neutrophils in epithelium = < 25% crypts involved |
| | **2** | Neutrophils in epithelium = ≥ 25% to ≤ 75% crypts involved |
| | **3** | Neurtrophils in epithelium = > 75% crypts involved |
| **Moderate** | **4** | Lamina propria neutrophils = Mild but unequivocal increase |
| | **5** | Lamina propria neutrophils = Moderate increase |
| | **6** | Lamina propria neutrophils = Marked increase |
| **Severe** | **7** | Erosion or ulceration = Present |

## 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.

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), GlaxoSmithKline and Third Party Resource. Concentrations of GSK2982772 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 has been analyzed for GSK2982772 any remaining plasma may be analyzed for other compound-related material and the results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

### 7.5.3. Colon Tissue Biopsy for Pharmacokinetic Assay

See Section 7.6.3 for more details on biopsies. Colonic tissue biopsies will be taken at Screening (on or prior to Day -7), Days 43 (Week 6) and 85 (Week 12) to measure the

concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible as sample availability allows.

#### 7.5.4. Sample Analysis

Colon tissue biopsy sample analysis will be performed under the control of PTS IVIVT, GlaxoSmithKline. Information on processing the tissue biopsies for the colonic 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 Biomarkers

#### 7.6.1. C Reactive Protein (CRP)

A blood sample will be taken as part of the chemistry laboratory sample to measure CRP at the time points indicated in Section 7.1. Information on sample processing will be provided in the laboratory manual.

#### 7.6.2. Faecal Calprotectin (FCP)

A faecal sample will be taken to measure faecal calprotectin at the time points indicated in Section 7.1. Information on sample processing will be provided in the laboratory manual.

#### 7.6.3. Tissue Biopsy

A total of 6 up to 12 (maximum) random biopsies will be taken throughout the inflamed sigmoid during the sigmoidoscopy at the screening visit (on or prior to Day -7), at pre-dose on Day 43 (Week 6) and on Day 85 (Week 12). Tissue samples will be divided accordingly for histological assessment (e.g., Geboes Index and MRS), PK, target and pathway engagement, and gene expression analyses as feasibility dictates. A variety of techniques including q-PCR, mRNA profiling and immunohistochemistry (IHC) may be used. Details of biopsy sample collection processing, storage and shipping procedures are provided in the laboratory manual).

mRNA may be isolated from tissue biopsies, 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 IL-1, IL-6, IL-8, MMP3, TNFα, IFNγ 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 analyses include, but are not limited to, quantitative PCR, microarray, and RNA sequencing.

Also see SRM for full details of the division of biopsy tissues for specific analyses.

### 7.6.4. Novel Pharmacodynamic Biomarkers

#### 7.6.4.1. 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.

#### 7.6.4.2. RIP1 Target Engagement in BiopsyTissue

Colon 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.

#### 7.6.4.3. Pathway Biomarkers in Biopsy Tissue

Colon 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.

### 7.6.5. 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 PK or 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 UC 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 colon tissue 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 blood and/or colon 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 up to 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 genetic 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

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 through week 6 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 parameters.

### 9.1. Sample Size Considerations

#### 9.1.1. Sample Size Assumptions

The study is not powered to detect pre-defined differences. Approximately 30-36 subjects will be randomised into the study to either GSK2982772 or placebo in a 2:1 ratio. Prior to protocol amendment 01 being approved in each country, subjects will be randomised into the study to either GSK2982772 60 mg BID or placebo in a 2:1 ratio. Overall up to 48 subjects will be randomised into the study to either a BID or TID regimen in a 2:1 ratio of GSK2982772 or placebo respectively. Table 8 summarises the total planned sample sizes

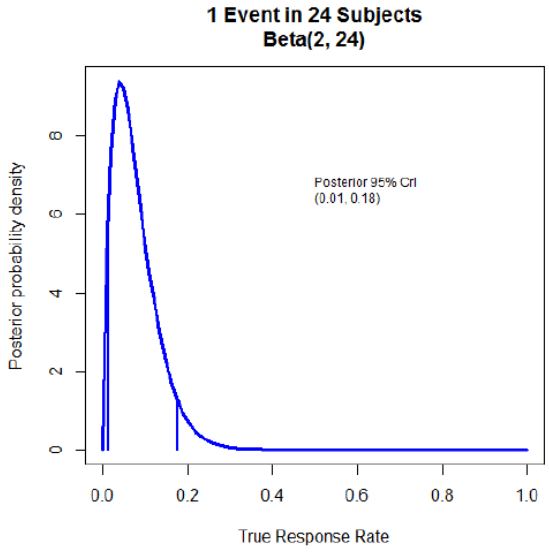
for BID and TID regimens. Should the dropout rate in Part A [Day 1 through 43 (Week 6)] be higher than anticipated, additional or replacement subjects may be randomised (up to an overall total maximum of 60) into the study at the discretion of the Sponsor. Subjects who discontinue participation during the open label phase in Part B [(Day 43 (Week 6) through Day 85 (Week 12)] will not be replaced.

**Table 8 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 60 mg | Revised Max Total Sample Size | Total + Additional/ Replacement Subjects |
|---|---|---|---|
| 0 - 6 | 30 - 36 | 36 | 48 |
| 7 - 12 | 30 - 36 | 42 | 54 |
| 12 - 18 | 30 - 36 | 48 | 60 |

The primary objective of the study is safety and tolerability, where there will be up to 24 subjects randomised to GSK2982772 60 mg TID, and up to 12 subjects randomised to GSK2982772 60 mg BID in Part A. Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 24 then the posterior distribution would be Beta (2, 24), as outlined below in Figure 4.

**Figure 4 One Event in 24 Subjects: Beta (2,24) Distribution**




Thus, we can be 95% certain that the true probability of the safety event lies between 0.01 and 0.18.

### 9.1.2. 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 24 in the GSK2982772 60 mg TID group, then the true incidence rates of the safety events that could not be ruled out (as outlined in Section 9.1.1) would change. These changes are outlined in Table 9.

**Table 9 Sample Size Sensitivity**

| GSK2982772 subjects completing the study | Number of a particular safety event observed with GSK2982772 | Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out |
|---|---|---|
| 24 | 0 | 13.7% |
| 24 | 1 | 20.4% |
| 24 | 2 | 26.0% |
| 20 | 0 | 16.1% |
| 20 | 1 | 23.8% |
| 20 | 2 | 30.4% |
| 16 | 0 | 19.5% |
| 16 | 1 | 28.7% |
| 16 | 2 | 36.4% |

### 9.1.3. Sample Size Re-estimation or Adjustment

A formal sample size re-estimation will be conducted at the planned Interim Analyses with the purpose of the assessing the probability of achieving a clinically meaningful increase in pre-determined clinical endpoints over placebo at the end of the study. The sample size may need to be re-estimated if higher variability or differing placebo means are observed on these endpoints. A recommended increase in sample size above 60 randomised subjects would require a protocol amendment.

## 9.2. Data Analysis Considerations

### 9.2.1. 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 analyses will be conducted on the Safety population such that subjects receiving placebo can be included.

### 9.2.2. Interim Analysis

Two interim analyses 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 UC.

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), mucosal healing will be reviewed in an unblinded manner 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 reviews will be to monitor mucosal healing rates. On review of mucosal healing 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.

The timing of Interim Analysis #1 will either be on the recommendation of the Data Review Committee to assess futility based on 6 weeks of treatment, or when an appropriate number have completed 6 weeks of treatment, whichever is earliest. The purpose of the Interim Analysis would be to assess whether to stop the study for futility and, if appropriate, to perform a sample size re-estimation. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for UC.

The timing of Interim Analysis #2 will occur when an appropriate number have completed 12 weeks of treatment. 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 UC.

## 9.3. Key Elements of Analysis Plan

### 9.3.1. 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.

Safety data collected in Part A and Part B of the study will be combined and summarised according to treatment received for the first six weeks of treatment and overall. 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. Secondary Analyses

Efficacy, PD and biomarker data will be summarised for Part A, and supporting summaries and analyses, as appropriate, will be summarised for Part A and Part B combined, according to treatment received.

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 and changes in inflammatory markers be statistically analyzed using a MMRM analysis comparing GSK2982772 with placebo at each time point. The proportion of subjects achieving Mayo Endoscopy Remission (Scores of 0 or 1), will be statistically analysed using a GEE model comparing GSK2982772 with placebo at each time point if appropriate. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

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., Mayo Endoscopy Scores). 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.

### 9.3.3. 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 proportion of Mayo Endoscopic Remission (0 or 1) (i.e., comparatory 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).

#### 9.3.3.1. 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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- 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.
- 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.

## 11. REFERENCES

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

Dondelinger Y, Aguileta MA, Goossens V, Dubuisson C, Grootjans S, Dejardin E *et al.* RIPK3 contributes to TNFR1-mediated RIPK1 kinase-dependent apoptosis in conditions of cIAP1/2 depletion or TAK1 kinase inhibition. *Cell Death and Differentiation*, 2013;20:1381-92.

Dourmashkin RR, Davies H, Wells C, Shah D, Price A, O'Morain C et al. Epithelial patchy necrosis in Crohn's disease. *Human Pathology,* 1983;14:643-8.

Duprez L, Takahashi N, Van Hauwermeiren F, Vandendriessche B, Goossens V, Vanden Berghe T et al. RIP kinase-dependent necrosis drives lethal systemic inflammatory response syndrome. *Immunity,* 2011;35:908-18.

Feagan BG, Chande N, MacDonald JK. Are there any differences in the efficacy and safety of different formulations of Oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from Cochrane reviews. *Inflamm Bowel Dis*. 2013 Aug;19(9):2031-40.

Fratila OC, Craciun C Ultrastructural evidence of mucosal healing after infliximab in patients with ulcerative colitis. J Gastrointestin Liver Dis. 2010 Jun;19(2):147-53.

Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut*, 2000 Sep;47(3):404-9.

GlaxoSmithKline Document Number 2014N204126_02. Investigator Brochure for GSK2982772. Report Date 27-JAN-2017.

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

Günther C, Martini E, Wittkopf N, Amann K, Weigmann B, Neumann H et al. Caspase-8 regulates TNF-α-induced epithelial necroptosis and terminal ileitis. *Nature,* 2011;477:335-9.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology*. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3 2.

Humphries F, Yang S, Wang B, Moynagh P N. RIP kinases: key decision makers in cell death and innate immunity. *Cell Death & Differ*, 2015;22:225-236.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

Ofengeim D and Yuan J. Regulation of RIP1 kinase signaling at the crossroads of inflammation and cell death. *Nature Reviews Molecular Cell Biology,* 2013;14:727-36.

Regeling A, Imhann F, Volders HH, Blokzijl T, Bloks VW, Weersma RK et al. HSPA6 is an ulcerative colitis susceptibility factor that is induced by cigarette smoke and protects intestinal epithelial cells by stabilizing anti-apoptotic Bcl-XL. Biochim Biophys Acta. 2016 Jan 26. Pii:S0925-4439(16)30017-5.

Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut*. 2011 Jun;60(6):780-7.

Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut*. 1991;32:174-178.

Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ et al; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014 Jan;146(1):96-109.

Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012 Feb;142(2):257-65.

Seidelin JB, Coskun M, Vainer B, Riis L, Soendergaard C, Nielsen OH et al. ERK controls epithelial cell death receptor signaling and cellular FLICE-like inhibitory protein (c-FLIP) in ulcerative colitis. *Journal of Molecular Medicine,* 2013;91:839-49.

Seidelin JB. Regulation of antiapoptotic and cytoprotective pathways in colonic epithelial cells in ulcerative colitis. *Scand J Gastroenterol*. 2015;50 Suppl 1:1-29.

Sipos F, Molnár B, Zágoni T, Berczi L, Tulassay Z. Growth in epithelial cell proliferation and apoptosis correlates specifically to the inflammation activity of inflammatory bowel diseases: ulcerative colitis shows specific p53- and EGFR expression alterations. *Dis Colon Rectum*. 2005 Apr;48(4):775-86.

Travis S, Schnell D, Krzeski P, Abrue MT, Altman DG, Colombel JF et al. Developing an instrument to assess endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut*, 2012 Apr;61(4):535-42.

U.S. Department of Health and Human Services, Food and Drug Administration (FDA). (2012) Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Center for Drug Evaluation and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

Vitali R, Stronati L, Negroni A, Di Nardo G, Pierdomenico M, Del Giudice E et al. Fecal HMGB1 is a novel marker of intestinal mucosal inflammation in pediatric inflammatory bowel disease. *American Journal of Gastroenterology.,* 2011;106:2029-40.

Wang L, Du F, Wang X. TNF-alpha induces two distinct caspase-8 activation pathways. *Cell*, 2008; 133(4):693-703.

Welz PS, Wullaert A, Vlantis K, Kondylis V, Fernandez-Majada V, Ermolaeva M et al. FADD prevents RIP3-mediated epithelial cell necrosis and chronic intestinal inflammation. *Nature,* 2011;477:330-4.

# 12. APPENDICES

## 12.1. Appendix 1– Abbreviations and Trademarks

### Abbreviations

| | |
|---|---|
| 5-ASA | 5-aminosalicylates |
| ADA | Anti-drug Antibodies |
| AE | Adverse Event |
| ALT | Alanine aminotransferase (SGPT) |
| AMD | Age-related macular degeneration |
| 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 |
| CL | Systemic Clearance |
| 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 |
| DNA | Deoxyribose Nucleic Acid |
| DPU | Discovery Performance Unit |
| DRC | Data Review Committee |
| ECG | Electrocardiogram |
| EDL | Early Development Lead |
| EMA | European Medicines Agency |
| ETCO2 | End-tidal Carbon Dioxide |
| FCP | Faecal Calprotectin |
| FDA | Food and Drug Administration |
| FRP | Females of Reproductive Potential |
| FSH | Follicle Stimulating Hormone |
| FTiH | First Time in Human |
| GCP | Good Clinical Practice |
| GEE | Generalised Estimating Equations |
| GFR | Glomerular Filtrate Rate |
| GSK | GlaxoSmithKline |
| 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 |
| IBD | Inflammatory Bowel Disease |
| ICH | International Conference on Harminisation |
| IDSL | Integrated Data Standards Library |
| IEC | Independent Ethics Committee |
| IFN | Interferon |
| IgG | Immunoglobulin gamma |
| IL | Interleukin |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IRTS | Interactive Response Technology System |
| Kg | Kilogram |
| L | Litre |
| LDL | Low Density Lipoprotein |
| MCH | Mean corpuscular haemoglobin |
| MCV | Mean Corpuscular Volume |
| MCHC | Mean corpuscular haemoglobin concentration |
| MDMA | 3,4-methylenedioxy-methamphetamine |
| 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 |
| MRS | Modified Riley Scale |
| msec | millisecond |
| MSD | Meso-Scale Discovery |
| 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 |
| NSAID | Non-steroidal anti-inflammatory drugy |
| NTI | Narrow therapeutic index |
| PCR | Polymerase Chain Reaction |
| PD | Pharmacodynamic |
| PGA | Physician's Global Assessment of Disease |
| P-gp | P-glycoprotein |
| PGx | Pharmacogenetic |
| 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 |
| PTS IVIVT | Platform Technology and Science In vitro/In vivo 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 |
| R&D | Research and Development |
| RAP | Reporting and Analysis Plan |
| RBC | Red Blood Cell |
| RCT | Randomised clinical trials |
| RIP1 | Receptor-interacting protein-1 |
| RIP3 | Receptor-interacting protein-3 |
| RNA | Ribonucleic Acid |
| SAE | Serious Adverse Event |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| 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 |
| TI | Terminal ileum |
| TID | Three times a day |
| TLR | Toll-like receptor |
| TNF | Tumor necrosis factor |
| TTS | Technical Terms of Supply |
| UC | Ulcerative colitis |
| UK | United Kingdome |
| ULN | Upper Limit of Normal |
| V | Volume of Distribution |
| VAS | Visual Analogue Scale |
| WCBP | Women of Childbearing Potential |

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## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| NONE |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| MedDRA |
| QuantiFERON |

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

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

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

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

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

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

| | |
|---|---|
| treatment and may continue subject in the study for any protocol specified follow up assessments<br><br>**MONITORING:**<br><br>**For bilirubin or INR criteria:**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**<br>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline<br>• A specialist or hepatology consultation is recommended<br><br>**For All other criteria:**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs**<br>• 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.<br>• Record alcohol use on the liver event alcohol intake case report form<br><br>**For bilirubin or INR criteria:**<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).<br>• 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**<br>• 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 and 5-ASA Equivalent Dose Tables

| **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 |
| **Drug Name** | **Dose Equivalent to ≤ 20 mg Oral Prednisone** |
| Uceris ER | 9 mg |
| **Drug Name** | **Dose Equivalent to 5-ASA** |
| Sulfasalazine | 2-4 g (0.8 – 1.6 gm 5-ASA) |
| Balsalazide | 2-6.75 g (0.7 – 2.4 gm 5-ASA) |

## 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;
- Ulcerative colitis susceptibility, severity, and progression and related conditions

GSK2982772 is a novel first-in-class asset being introduced to patients with active UC 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, 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 analyzed during the study or stored for future analysis.

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

### Screen and Baseline Failures

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

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

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not

known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

## 12.5. 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.<br>• 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.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected interaction.<br>• 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).<br>• "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.<br>• 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.<br>• 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.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.<br>• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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**<br>NOTE:<br>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**<br>NOTE:<br>• 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.<br>• 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**<br>NOTE:<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• 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:**<br>• 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.<br>• 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:**<br>• ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**<br>• ALT ≥ 3xULN and INR** > 1.5.<br>* 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.<br>** 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:<br>• Myocardial infarction/unstable angina<br>• Congestive heart failure<br>• Arrhythmias<br>• Valvulopathy<br>• Pulmonary hypertension<br>• Cerebrovascular events/stroke and transient ischemic attack<br>• Peripheral arterial thromboembolism<br>• Deep venous thrombosis/pulmonary embolism<br>• 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.<br>• The Investigator will then record all relevant information regarding an AE/SAE in the CRF<br>• 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.<br>• 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.<br>• 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.<br>• Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.<br>• Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. |

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

### 12.5.5. 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.

Contraceptive subdermal implant

1. Intrauterine device or intrauterine system
2. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
3. Injectable progestogen [Hatcher, 2011]
4. Contraceptive vaginal ring [Hatcher, 2011]
5. Percutaneous contraceptive patches [Hatcher, 2011]
6. 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.

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 5. 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

Protocol Amendment 1 (20-APR-2017) from the original protocol (23-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**

Change in dosing regimen from 60 mg BID to 60 mg TID, updates to Inclusion criteria 3 and 6 and Exclusion criteria 3, 9, 21 and 22, allowance for rescreening and addition of suicidality stopping criteria.

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<br>**Email** PPD<br>~~Tel:~~ PPD<br>~~Mobile:~~ PPD<br>~~Email:~~ PPD | **Mobile** PPD<br>~~Mobile:~~ PPD | **N/A**<br>PPD | **GSK Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, UK**<br>~~Pattern Recognition Receptor DPU, UP4440 1250 S Collegeville, PA 19426~~ |

| | | | | | |
|---|---|---|---|---|---|
| Secondary Medical Monitor | PPD | **Mobile:** ~~+~~PPD **Email** PPD ~~Tel:~~ PPD ~~Mobile:~~ PPD ~~Email:~~ PPD | **Mobile:** PPD ~~Mobile:~~ PPD | **NA** | **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 01; however the dosing regimen does change to GSK2982772 (60 mg three times daily for both Parts A and B).**

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 60 mg or placebo ~~twice~~**three times** daily for 42 days (Part A) followed by open label with GSK298772 60 mg ~~twice~~**three times** daily for 42 days (Part B). In addition to 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 UC. 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 UC, 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 active ulcerative colitis. | • Adverse events.<br>• Clinical laboratory values (clinical chemistry, haematology and urinalysis).<br>• Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature).<br>• 12-Lead ECG monitoring. |
| **Secondary** | |
| • To investigate the preliminary efficacy of 60 mg ~~twice~~**three times** daily doses of GSK2982772 in achieving mucosal healing after 6 and 12 weeks of treatment in subjects with active | • The proportion of subjects who achieve an absolute Mayo endoscopy subscore of 0 or 1 at Days 43 (Week 6) and 85 (Week 12).<br>• Change from baseline in mucosal |

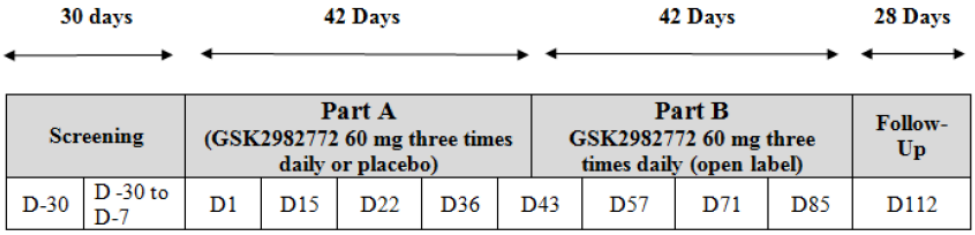
| Objectives | Endpoints |
|---|---|
| ulcerative colitis. | appearance determined by Ulcerative Colitis Endoscopic Index of Severity (UCEIS). |
| • To investigate the effect of 60 mg ~~twice~~**three times** daily doses of GSK2982772 on biomarkers of disease activity in subjects with active ulcerative colitis. | • Change from baseline in markers which may include, but are not limited to, mean CRP and faecal calprotectin (FCP). |
| • To investigate the effect of 60 mg ~~twice~~**three times** daily doses of GSK2982772 on histologic disease activity in subjects with active ulcerative colitis. | • Change from baseline in histologic severity, including but not limited to Modified Riley Score and Geboes Index. |
| • To investigate the effect of 60 mg ~~twice~~**three times** daily doses of GSK2982772 in achieving clinical response and remission after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • The proportion of subjects who achieve clinical response defined as reduction by ≥3 points or ≥30% improvement from baseline complete Mayo score, along with a decrease in the rectal bleeding score of ≥1 point, at Days 43 (Week 6) and 85 (Week 12).<br>• The proportion of subjects who achieve clinical remission defined as a complete Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, at Days 43 (Week 6) and 85 (Week 12). |
| • To investigate the preliminary efficacy of 60 mg ~~twice~~**three times** daily doses of GSK2982772 in achieving symptomatic clinical remission after 6 and 12 weeks of treatment in subjects with active ulcerative colitis. | • Change from baseline in partial Mayo score. |
| • To investigate the plasma concentrations of GSK2982772 following 60 mg ~~twice~~**three times** daily in subjects with active ulcerative colitis. | • Pre-dose plasma concentrations of GSK2982772 at Day 43 (Week 6).<br>• Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours.<br>• Trough concentrations on Day 85 (Week 12). |
| **Exploratory** | |
| • To investigate the effect of 60 mg ~~twice~~**three times** daily doses of GSK2982722 on expression of | • Change from baseline in inflammatory markers which may include, but are not limited to IL-1, IL-6, IL-8, MMP3, TNFα, |

| Objectives | Endpoints |
|---|---|
| inflammatory biomarkers in mucosal tissue biopsies in subjects with active ulcerative colitis. | IFNγ. |
| • To investigate pathway and target engagement following 60 mg ~~twice~~**three times** daily doses of GSK2982772 in blood and colon biopsy tissue. | • 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:<br>○ Target Engagement Assay RIP1 (TEAR1) in blood and colon tissue.<br>○ Phosphorylated or total RIP1, MLKL, RIP3, cleaved and total caspase 3 and caspase 8 signatures in colon tissue. |
| • To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the colon tissue after 60 mg ~~twice~~**three times** daily doses of GSK2982772. | • Pre-dose GSK2982772 and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, in colon biopsies at Days 43 (Week 6) and 85 (Week 12), as evaluable samples and data permit. |
| • To investigate the effect of 60 ~~twice~~**three times** daily doses of GSK2982772 on quality of life in subjects with active ulcerative colitis. | • Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ). |
| • To investigate the effect of 60 ~~twice~~**three times** daily doses of GSK2982772 on gene expression in the blood subjects with active ulcerative colitis. | • Transcriptomic analysis of mRNA isolated from blood 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 colon tissue biopsies in subjects with active ulcerative colitis. | • Transcriptomic analysis of mRNA isolated from colon tissue biopsies at Screening, and Days 43 (Week 6) and trough on Day 85 (Week 12). |

**Synopsis and Section 4.1 Overall Design**

**Schematic added.**

**Amendment 01:**




**Synopsis Treatment Arms and Duration**

Part A: Approximately 36 subjects who have completed screening assessments and are eligible will be randomized in a 2:1 ratio (active to placebo) to one of the following study treatments for 42 days:

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

Placebo ~~twice~~**three times** daily (~~B~~TID)

Part B: Is a 6 week open label extension where **all** subjects who have completed Part A will receive 60 mg GSK2982772 ~~twice~~**three times** daily (~~B~~**TID**) for 42 days.

**Prior to amendment 01 being effective in each country, subjects have been randomised in a 2:1 ratio (active to placebo) to one of the following treatments for Part A:**

**GSK2982772 60 mg twice daily (BID) x 42 days**

**Placebo twice daily (BID) x 42 days**

**Part B: A 6 week open label extension where all subjects who have completed Part A received 60 mg GSK2982772 twice daily (BID) for 42 days.**

**Synopsis and Section 4.3 Type and Number of Subjects**

A sufficient number of subjects will be screened so that approximately **30-36** subjects with active UC will be randomised into the study **on a TID regimen. Prior to protocol amendment 01 being approved in each country, no more than 18 subjects will be randomised into the study on a BID regimen**. Should the dropout rate in Part A [Day 1 through 43 (Week 6)] be higher than anticipated, or the sample size review warrants an increase in randomised subjects, additional or replacement subjects may be randomised (up to **an overall total** maximum of ~~48~~**60**) into the study at the discretion of the Sponsor. Subjects who discontinue participation during the open label phase in Part B [(Day 43 (Week 6) through Day 85 (Week 12)] will not be replaced.

**Section 4.2.2 Treatment Period**

Subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally ~~twice~~**three times** daily (approximately **8**~~12~~ hours apart) for 42 days (6 weeks) in a 2:1 ratio in Part A. All subjects will move to open label in Part B to receive GSK2982772 60 mg ~~twice~~**three times** daily (approximately**8**~~12~~ hours apart) for an additional 42 days (6 weeks). Treatment duration is a total of 84 days (12 weeks) inclusive of Parts A and B. **Subjects that were randomised prior to protocol amendment 01 being approved in each country were randomly assigned to either GSK2982772 60 mg or placebo orally two times daily (approximately 12 hours apart) for 42 days followed by GSK2982772 60 mg BID for 42 days.**

During the 84 day (12 week) treatment period, subjects will attend the clinical site for visits on Days 1, 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 8, 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 which will they will be instructed to record their daily study medication and concomitant medication administration and any adverse events.

**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 from the single dose ascending part of study 200975, a 60 mg BID dose **was**~~is~~ predicted to have on average 95% RIP1 target engagement and approximately 90% of subjects will have >90% target engagement 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 is currently available about the distribution of GSK2892772 into gastrointestinal (GI) tissue. ~~However, if blood concentration is representative of the concentration at the site of action, a 60 mg BID dose regimen should provide sufficient RIP1 target engagement to establish proof of mechanism.~~

**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. No subjects have been randomised yet to this study (Study 202152). 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 UC.~~

~~It is anticipated that a human dose of 60 mg BID will produce $AUC_{(0-24)}$ and $C_{max}$ values of approximately 9 ug.h/mL and 1 ug/mL, respectively, which are approximately $1/6^{th}$ and $1/12^{th}$ 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 NOAEL dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01].~~

**Section 5.1 Inclusion Criteria**

3. Subject has had a confirmed diagnosis of active UC, as documented by complete diagnostic colonoscopy to the terminal ileum **(TI)** with biopsy ~~at least~~ performed ≥ 3 months prior to screening. **If diagnostic colonoscopy was not performed to the TI, it must be documented by the PI that the subject has diffuse inflammation from the rectum extending proximally to the colon in a continuous and uniform way.**
6. Subject is naive to any biological therapies for UC.
   **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) prior to first dose.

**OR**
**Subject may have had previous exposure to a single biologic agent (e.g., vedolizumab) in the context of a previous clinical trial. The biologic agent must have been discontinued more than 8 weeks (or 5 half lives whichever is longer) prior to first dose.**
**Note: Exposure to a single biologic agent is not required in addition to Inclusion #4 and #5 above.**

**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**

3. Subject with previous small bowel or colonic surgery **(with exception of appendectomy)**, histological evidence of colonic dysplasia or bowel stricture.
9. QTc > 450msec or QTc > 480msec for subjects with bundle branch block at screening~~ and Day -1~~.
21. 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 **(not inclusive of any UC registry study where no study medication is being administered)** at the same time as participating in this clinical trial.
22. Haemoglobin <10 g/dL; haematocrit <30%, white blood cell count ≤3,000/mm3 (≤3.0 x $10^9$/L)~~ or ≥14,000/mm3 (≥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~~.

**Section 5.3 Screening/Baseline/Run-in Failures**

**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 (preferably before performing sigmoidoscopy), but the Investigator believes there is a reasonable probability that the subject would be eligible if re-screened.**

**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 medication for the treatment of UC 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 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 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 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

**Section 6.1 Investigation Product and Other Study Treatment**

| | 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 01):** | **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 01):** | 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**

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 **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 6.11.2 Prohibited Medications and Non-Drug Therapies**

**Table 2**

| Therapy | Time period |
|---|---|
| A change in dose of 5-ASA | 4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112) |
| A change in dose of purine analogue | 12 weeks prior to first dose (Day 1) until after the follow up visit (Day 112) |
| A change in dose of MTX | 12 weeks prior to first dose (Day 1) until after the follow up visit (Day 112). |
| Greater than 20mg/day oral prednisolone (or equivalent corticosteroid) or a change in dose of corticosteroid. | 2 weeks prior to sigmoidoscopy until after the follow up visit (Day 112). |
| A change in dose or frequency of topical (rectal) corticosteroids or topical (rectal) 5-ASA. | 4 weeks prior to first dose (Day 1) until after the follow up visit (Day 112). |
| Exposure to more than one anti-TNF biologic therapy including but not limited to anti-TNF biologics, infliximab, adalimumab, and golimumab.<br><br>**Exception**: Exposure to a single anti-TNF-biologic for which the subject the subject discontinued for a reason other than primary non-response. | Cannot have been exposed to more than 1 anti-TNF biologic or be on biologic therapy at any time during the study.<br><br>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). |
| ~~Biologic therapies~~**Exposure to a single biologic** therapy for the treatment of UC **(other than anti-TNF as detailed above), including** but not limited to vedolizumab.<br>**Exception**: **vedolizumab previously administered in a clinical trial setting.** | Cannot have been on at any time, **except for vedolizumab in a clinical trial setting where it must have been discontinued for 8 weeks or 5 half lives (whichever is longer) prior to first dose.** |

## Section 7.1 Time and Events Table

| Procedures | Screening (-30) | Screening (-7 to -30) | Treatment Period[18] | | | | | | | | | | | | | Early Withdrawal[19] | Follow Up (±3)[20] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PART A | | | | | | | PART B | | | | | | | |
| | | | 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 | | 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[4] | | X | | X | | X | X | X |
| 12-lead ECG[3] | X | | X[4] | | X | | X | | X[4] | | X | | X | | X | X | X |
| Concomitant medication review & AE reporting/SAEs[5] | | | X---------- | | | | | | | | | | | | | | ----------X |
| **PROs/Questionnaires/Disease Assessments and Procedures** | | | | | | | | | | | | | | | | | |
| Columbia Suicide Severity Rating Scale (C-SSRS) | X | | X[4] | | | | | | X[4] | | | | | | X | X | |
| IBDQ[6] | | | X[4] | | | | | | X[4] | | | | | | X | X | |
| UCEIS, Modified Riley, Geboes | X-------X[7] | | | | | | | | X[4] | | | | | | X | **X** | |

| Procedures | Screening (-30) | Screening (-7 to -30) | Treatment Period[18] | | | | | | | | | | | | | Early Withdrawal[19] | Follow Up (±3)[20] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PART A | | | | | | | PART B | | | | | | | |
| | | | 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) | | |
| Mayo Score (including sigmoidoscopy and biopsy) | X-----X[7] | | | | | | | | X[4, 8] | | | | | | X | X[9] | |
| Partial Mayo Score | X-----X[7] | | | | X | | X | | X[4] | | | | | | X | X | |
| **Study Treatment** | | | | | | | | | | | | | | | | | |
| Randomisation | | | X | | | | | | | | | | | | | | |
| Study medication (~~twice~~**three times** daily)[10] | | | X----------XX----------X[11] | | | | | | | | | | | | | | |
| Dispensing of study medication | | | X | | X | | | | X | | | | | | | | |
| Dispensing of diary cards | | | X | | X | | X | | X | | X | | X | | | | |
| Collection of diary cards | | | | | X | | X | | X | | X | | X | | X | | |
| **Laboratory (Safety) Assessments and Procedures** | | | | | | | | | | | | | | | | | |
| TB, HIV, Hep B, Hep C Ab, C. Difficile toxin | X | | | | | | | | | | | | | | | | |
| FSH & estradiol (if applicable) | X | | | | | | | | | | | | | | | | |
| Serum pregnancy test (WCBP only) | X | | | | | | | | | | | | | | | | |
| Urine pregnancy test (WCBP only)[12] | | | X[4] | | X | | X | | X[4] | | X | | X | | X | X | X |
| Haematology, chemistry, urinalysis | X | | X[4] | | X | | X[13] | | X[4] | | X[13] | | X[13] | | X | X | X |
| Faecal calprotectin[14] | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Blood sample for exploratory | | | X[4] | | | | | | X[4] | | | | | | X | X | |

| Procedures | Screening (-30) | Screening (-7 to -30) | Treatment Period[18] | | | | | | | | | | | | | Early Withdrawal[19] | Follow Up (±3)[20] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PART A | | | | | | | PART B | | | | | | | |
| | | | 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) | | |
| biomarkers and TE[15] | | | | | | | | | | | | | | | | | |
| PK blood samples GSK2982772[16] | | | X | | | | | | X[4] | | | | | | X | X | |
| Biopsies for PK, inflammatory biomarkers, mRNA, TE & pathway marker analysis | X-------X[7] | | | | | | | | X[4] | | | | | | X | X[8] | |
| Pharmacogenetic sample (PGx)[17] | | | X | | | | | | | | | | | | | | |

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. PRO assessments should be conducted before any tests, procedures or assessments to avoid influencing the subjects' perception.
7. Sigmoidoscopy may be performed at any time during the screening window as an additional visit (if required) up to Day -7 in order for central reading confirmation of Mayo Score for inclusion. **If a shorter window is required (e.g., within Day -3 to Day -7), this will be permitted as long as it has been confirmed with the sponsor and central reader that results of the Mayo endoscopy score will be available before end of the screening window.** Histological disease (e.g., UCEIS, MRS and Geboes Index) along with Mayo score assessments will also be completed.
8. Sigmoidoscopy may be performed on a separate day within the Day 43 visit window allowance (±3 days). A separate visit to perform sigmoidoscopy is only allowed to accommodate scheduling. This separate visit **should~~can~~** be done before~~ or after~~ the full Day 43 visit where PK, clinical laboratory tests and all other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the sigmoidoscopy procedure and also the morning before the full Day 43 visit, if being done on a separate day. Dispensing of study medication must be done at the 2nd visit (if separate visits are performed).
9. Biopsy only required at Early Withdrawal visit if after at least 14 days of treatment and prior to Day 43 or if after Day 57 and prior to Day 85.

10. 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 43 and 85, subjects must not take their study medication at home in the morning. Subjects will complete specified pre-dose assessments and then will be administered their morning dose of medication at site on Day 43. On Day 85, subjects are no longer receiving study medication.
11. In Part A, subjects will be randomised 2:1 to GSK298722 60 mg or placebo ~~twice~~**three times** daily for 42 days. At the Day 43 visit, all subjects who have completed Part A, will move in to Part B open label treatment with GSK2982772 60 mg ~~twice~~**three times** daily for 42 days.
12. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
13. Urinalysis not required on Days 29, 57 and 71.
14. Subjects can provide a faecal sample at any time during the screening window and up to 48 hours prior to any visit where FCP is being collected. Please see laboratory manual for full details on sample handling and procedure.
15. Blood samples for exploratory biomarkers and Target engagement. See laboratory manual for full details on sample collection, handling and shipment.
16. PK blood samples for GSK2982772 will be taken pre-dose on Day 43. Post-dose serial PK samples will be taken on Days 1 and Day 43 at the following time points: 1, 2, 4, and 6 hours and trough on Day 85 or Early Withdrawal.
17. A PGx blood sample is collected at the baseline visit (Day 1), after the subject has been randomized 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 randomization.
18. Visit windows during the treatment period are relative to Day 1.
19. 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.
20. Follow-up visit should be completed 28 days (±3 days) after the last dose of study medication.

**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 GSK2982722 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.~~ **Study medication must be immediately discontinued in a~~All~~ subjects who experience signs of suicidal ideation or behaviour.**

**Section 7.4.2.1 Mayo Score**

**Table 4**

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

**Section 9.1.1 Sample Size Assumptions**

The study is not powered to detect pre-defined differences. Approximately **30**-36 subjects will be randomised into the study to either GSK2982772 or placebo in a 2:1 ratio. **Prior to protocol amendment 01 being approved in each country, subjects will be randomised into the study to either GSK2982772 60 mg BID or placebo in a 2:1 ratio. Overall up to 48 subjects will be randomised into the study to either a BID or**

**TID regimen in a 2:1 ratio of GSK2982772 or placebo respectively. Table 8 summarises the total planned sample sizes for BID and TID regimens.** Should the dropout rate in Part A [Day 1 through 43 (Week 6)] be higher than anticipated, additional or replacement subjects may be randomised (up **to an overall total** maximum of **60~~48~~**) into the study at the discretion of the Sponsor. Subjects who discontinue participation during the open label phase in Part B [(Day 43 (Week 6) through Day 85 (Week 12)] will not be replaced.

**Table 8 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 60 mg | Revised Max Total Sample Size | Total + Additional/ Replacement Subjects |
|---|---|---|---|
| 0 - 6 | 30 - 36 | 36 | 48 |
| 7 - 12 | 30 - 36 | 42 | 54 |
| 12 - 18 | 30 - 36 | 48 | 60 |

The primary objective of the study is safety and tolerability, where there will be up to 24 subjects randomised to **GSK2982772 60 mg TID, and up to 12 subjects randomised to GSK2982772 60 mg BID** in Part A. Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in **24~~20~~** then the posterior distribution would be Beta (2, 24), as outlined below in Figure 4.

**Section 9.1.2 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 24 in the GSK2982772 **60 mg TID** group, then the true incidence rates of the safety events that could not be ruled out (as outlined in Section 9.1.1) would change. These changes are outlined in Table 9.

**Section 9.1.3 Sample Size RE-estimation of Adjustment**

A formal sample size re-estimation will be conducted at the planned Interim Analyses with the purpose of the assessing the probability of achieving a clinically meaningful increase in pre-determined clinical endpoints over placebo at the end of the study. The sample size may need to be re-estimated if higher variability or differing placebo means are observed on these endpoints. A recommended increase in sample size above **60~~48~~** randomised subjects would require a protocol amendment.

**Section 9.2.2 Interim Analysis**

Once an appropriate number of subjects have completed Day 43 (Week 6), mucosal healing will be reviewed in an unblinded manner 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. The primary purpose of these reviews will be to monitor mucosal healing rates. On review of mucosal healing 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.

**Section 9.3.1 Primary Analyses**

Safety data collected in Part A and Part B of the study will be combined and summarised according to treatment received for the first six weeks of treatment and overall. **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 11 References**

GlaxoSmithKline Document Number 2014N204126_~~01~~**02**. Investigator Brochure for GSK2982772. Report Date ~~08 MAR 2016~~**27-JAN-2017**.

**Section 12.1 Appendix 1 – Abbreviations and Trademarks**

| | |
|---|---|
| **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** |
| **TI** | **Terminal ileum** |
| **TID** | **Three times daily** |

**Section 12.3 Appendix 3:** Prednisolone and **5-ASA** Equivalent Dose Tables

| **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 |
| **Drug Name** | **Dose Equivalent to ≤ 20 mg Oral Prednisone** |
| **Uceris ER** | **9 mg** |
| **Drug Name** | **Dose Equivalent to 5-ASA** |
| **Sulfasalazine** | **2-4 g (0.8 – 1.6 gm 5-ASA)** |
| **Balsalazide** | **2-6.75 g (0.7 – 2.4 gm 5-ASA)** |

**Section 12.4 Appendix 4 – Genetic Research**

**GSK2982772 is a novel first-in-class asset being introduced to patients with active UC 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.