TITLE PAGE

Protocol Title: A two part, non-randomised, open label study designed to assess the pharmacokinetic profile of modified release prototype coated tablet formulations of GSK2982772 relative to an immediate release reference tablet formulation at a fixed strength (Part A) and the pharmacokinetic profile of alternative tablet strengths of the selected modified release prototype coated tablet formulation (Part B, optional) in healthy participants.

Protocol Number: 209261/Amendment 3

Quotient Reference Number: QSC201113

Short Title: A study to investigate the pharmacokinetics of modified release prototype coated tablet formulations of GSK2982772.

Compound Number: GSK2982772

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Communication Plan

Regulatory Agency Identifying Number(s): EudraCT Number 2018-002370-48

Approval Date: 10-APR-2019

SPONSOR SIGNATORY:

PPD

16/04/19

Simon Hawkins, MD
Project Physician Leader GSK2982772, GSK R&D

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 3	10-APR-2019	2018N367092_04
Amendment 2	26 FEB-2019	2018N367092_03
Amendment 1	28-AUG-2018	2018N367092_02
Original Protocol Republishing	08-AUG-2018	2018N367092_01
Original Protocol	23-JUL-2018	2018N367092_00

Amendment 3 10-APR-2019

Overall Rationale for the Amendment:

This amendment will incorporate an additional optional period (Period 7) to Part B of the study. This additional period will incorporate the additional options for a delayed high-fat or standard breakfast/evening meal given 30 min to 60 min post-dose and/or morning or evening dosing.

Section # and Name	Description of Change	Brief Rationale
Synopsis – Objectives and Endpoints, Overall Study Design and Treatment Groups and Duration, Table 1 – Schedule of Activities for Parts A and B, Table 2 – Pharmacokinetic Blood Sample Collection Times – Part A and B, Section 3.3 – Benefit/Risk Assessment, Section 4 - Objectives and Endpoints, Section 5.1 – Overall Design, Section 5.1.2 – Part B, Figure 2 – Part B Study Design – Tablet Strength, Section 5.1.3 – Criteria for Interim Decisions, Section 5.4 – Scientific Rationale for Study Design, Section 6.3.1 – Meals and Dietary Restrictions, Section 7.1.2 – Treatments Administered – Part B, Section 9 – Study Assessments and Procedures, Section 10.4.1 –	An additional optional Period (Period 7) has been added to Part B. The clinical protocol currently only allows for dosing in the morning of Day 1 in each period and administering a standard high-fat breakfast pre-dose. The protocol will be updated to allow dosing in the evening and the potential for dosing a high-fat breakfast or evening meal 30 to 60 minutes post-dose (for Part B Period 7 only).	Based on emerging data from Part B, the sponsor (GSK) would like the opportunity to investigate whether the between-subject variability in absorption time following administration of 480 mg tablet with a standard high-fat breakfast (administered in previous periods) can be reduced by changing feeding regimen or time of administration in an additional optional period (Period 7) to Part B of the study. This additional period will allow for the possibility of a delayed breakfast or evening meal at 30 or 60 minutes post-dose, morning or evening dosing and/or administration after a standard or high-fat breakfast or evening meal.

Section # and Name	Description of Change	Brief Rationale
Pharmacokinetic Analyses and Section 10.4.3 – Interim Analyses		

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A two part, non-randomised, open label study designed to assess the pharmacokinetic profile of modified release prototype coated tablet formulations of GSK2982772 relative to an immediate release reference tablet formulation at a fixed strength (Part A) and the pharmacokinetic profile of alternative tablet strengths of the selected modified release prototype coated tablet formulations (Part B, optional) in healthy participants.

Short Title: A study to investigate the pharmacokinetics of modified release prototype formulations of GSK2982772.

Rationale: Previous clinical studies of immediate release (IR) formulations of GSK2982772 resulted in a high peak:trough ratio of GSK2982772. Additionally, the short half-life for GSK2982772 (~2 to 3 hours) necessitates twice daily (BID) or three times daily (TID) dosing of an IR formulation. As a result, modified release (MR) formulations using a polymer matrix approach with minitablets in capsule and MR tablet formulations were investigated. The emerging pharmacokinetic (PK) data of the MR formulations investigated to date have demonstrated that a once daily (QD) PK profile can be achieved in the fasted state but the polymer matrix formulation is susceptible to food effects when administered with a high-fat breakfast. The purpose of this study is to evaluate MR prototype coated tablet formulations. The MR coated tablet formulation uses a combination of a controlled-release polymer matrix and controlled-release coating to achieve a modified-release of the drug. The MR tablet coating used in Part A and the initial periods of Part B will have an aperture drilled into the enteric coating of either side of the tablet. This allows some drug release to commence in the stomach whilst providing a controlled release throughout the GI tract. This MR tablet coating has been used in other formulations (e.g. Lamictal XR) and in vivo has shown robustness against food effects. The hypromellose (HPMC) polymer has been shown to be effective in achieving a controlled delay to the drug release rate and thus lowering the maximum observed concentration (C_{max}) and increasing the concentration at 24 hours post-dose (C_{24h}) of the product. However, it is believed that the digestive mechanical action that the dosage form is exposed to in the fed stomach, and/or the longer stomach retention time when dosed in the fasted state, causes an increase in the rate of drug release. Application of an enteric coating with apertures will control the release rate when in the stomach. In Part B only, a new IMP will be manufactured to allow comparison of the tablet coating either with apertures (i.e., drilled) or without apertures (i.e., full coat/non-drilled).

Part A of the study is an adaptive crossover study that will optimise the MR prototype coated tablet formulation to provide a formulation suitable for QD dosing and has no clinically significant food effect. The MR prototype coated tablet formulations have a matrix core containing hypromellose polymers. The MR prototype coated tablet formulations will be optimised within a one-dimensional design space where release rate from the tablet will be adjusted by varying the polymer ratio in the tablet core. The polymers will be hypromellose 2208 K3LV (polymer 1) and/or K100LV (polymer 2) and/or K4M (polymer 3). The dose will be fixed at 240 mg, and the in vitro release rate will be targeted such that the tablet core of GSK2982772 MR prototype coated tablet

formulation MR1 will have a dissolution profile that is similar to the release rate of the slowest release MR minitab formulation from Study 205017 (approximately 80% in vitro release at 12 hours). GSK2982772 MR prototype coated tablet formulation MR2 will be designed such that the in vitro dissolution is slower than that of MR1, and will be the slowest available within the design space. If neither MR1 nor MR2 provide an optimal profile, further MR prototype coated tablet formulations will be investigated. The impact of food on the PK of GSK2982772 will also be evaluated for the selected formulation(s). After completion of Periods 3, 4 and 5, interim analyses will be conducted to determine the formulation and prandial status to be investigated in the next period. After completion of Part A, an interim analysis will be conducted to identify the MR prototype coated tablet formulation(s) for progression into Part B. If none of the MR prototype coated tablet formulations are suitable, then Part B of the study may not be conducted or Part B may be used to continue to optimise the formulation, which may include varying the tablet coating either with apertures (i.e., drilled) or without apertures (i.e., full coat/non-drilled) by the manufacture of a new IMP.

Optional Part B will assess the pharmacokinetics of alternative tablet strengths (120 mg and 480 mg, or alternative strengths) as allowed by the design space or tablets with apertures (i.e., drilled) or without apertures (i.e., full coat/non-drilled) or multiple dosing units of the optimum MR formulation selected from Part A. If the in-vivo profile of either or both the 120 mg or 240 mg tablets (or alternative strengths) differs from the optimal profile with the 240 mg, the ratio of the polymers K3LV, K100LV and/or K4M may be adjusted within each of the alternative strengths. In order to assess the effect of the aperture on the in vivo performance of the formulation, a fully coated tablet (i.e., without apertures) may be assessed in Part B, Period 3 onwards. If fully coated tablet(s) are dosed, the core composition will match a previously dosed formulation to allow a valid comparison. Prior to initiation of Part B, a substantial amendment to the investigational medicinal product dossier (IMPD), will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) for approval, to include updated information on the selected GSK2982772 MR prototype coated tablet formulations at alternative strengths.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each MR prototype coated tablet formulation (240 mg) compared to the IR formulation (240 mg) (Part A)	• GSK2982772 area under the curve from time zero to infinity ($AUC_{(0\text{-}inf)}$), area under the curve from time zero to the last measurable concentration ($AUC_{(0\text{-}t)}$), area under the curve from time zero to 24 hours ($AUC_{(0\text{-}24)}$), maximum observed concentration (C_{max}), concentration at 24 hours post-dose (C_{24h}), time to C_{max} (T_{max}), terminal half-life ($t_{1/2}$)

Objective	Endpoint
• To assess the impact of a high-fat breakfast on the PK of GSK2982772 following single dose administration of one or more selected MR prototype coated tablet formulations (240 mg) (Part A or Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max}, C_{24h}, and $t_{1/2}$, relative bioavailability ($FreI_{FE}$), relative bioavailability ($FreI_{Formulation}$), based on AUC and C_{max}
Secondary	
• To assess the safety and tolerability of single doses of GSK2982772 (Part A)	• Adverse events (AEs) • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead electrocardiogram (ECG) monitoring
• To determine the bioavailability of GSK2982772 MR prototype coated tablet formulations relative to the IR reference, as appropriate (Part A)	• Relative bioavailability ($FreI_{formulation}$) based on AUC and C_{max}
Exploratory	
• To assess the safety and tolerability of single doses of GSK2982772 (Optional Part B)	• Adverse events (AEs) • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead electrocardiogram (ECG) monitoring
• To evaluate the PK profile of alternative tablet strengths of selected GSK2982772 MR prototype coated tablet formulations (Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, C_{max}, C_{24h}, $t_{1/2}$, AUC/Dose and C_{max}/Dose
• To evaluate the impact of dosing 2 or more MR prototype coated tablets on the PK profile of GSK2982772 (Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$ or $AUC_{(0\text{-}24)}$, C_{max}, T_{max} and $t_{1/2}$

Objective	Endpoint
• To determine if there are any dose dependent changes in the absorption of GSK2982772 following single dose administration selected GSK2982772 MR prototype coated tablet formulations (Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, C_{max}, C_{24h} and T_{max}
• To assess the impact of a standard breakfast on the PK of GSK2982772 following single dose administration of one or more selected MR prototype coated tablet formulations (240 mg) (Part A - optional)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $t_{1/2}$, relative bioavailability ($Frel_{FE}$), relative bioavailability ($Frel_{Formulation}$), based on AUC and C_{max}
• To assess the impact of a delayed meal on the PK of GSK2982772 following single dose administration of one or more selected MR prototype coated tablet formulations (240 mg) (Part A - optional)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $t_{1/2}$, relative bioavailability ($Frel_{FE}$), relative bioavailability ($Frel_{Formulation}$), based on AUC and C_{max}
• To assess the impact of evening dosing (Optional Part B, Period 7 only) on the PK of GSK2982772 following single dose administration selected GSK2982772 MR prototype coated tablet formulations.	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $t_{1/2}$, relative bioavailability (Frel (time effect), based on AUC and C_{max}

Overall Design:

This is an open label, non-randomised single centre, two part, single dose study in healthy male and female participants to assess MR prototype coated tablet formulations of GSK2982772. The impact of food (high-fat breakfast) on the rate and extent of absorption will be evaluated for suitable MR prototype coated tablet formulations, and an assessment of alternative tablet strengths, dosing of multiple dose units and presence/absence of apertures in the tablet may also be performed. An assessment of a standard or high-fat breakfast/evening meal or study drug administration 30 or 60 minutes before a standard or high-fat (Part B, Period 7 only) breakfast or evening meal may also be included. The single dose may be given in the morning or evening (Part B, Period 7 only).

Part A of the study is a non-randomised up to 6 period, 6-way fixed sequence design in which up to 4 MR prototype coated tablet formulations may be evaluated following single dose administration in the fasted state (240 mg). Periods 1, 2 and 3 will evaluate MR1 (similar in vitro dissolution to the slowest minitab MR formulation from study 205017), IR tablet (240 mg) and MR2 (slower in vitro dissolution than MR1) respectively. Periods 4, 5 and 6 will be flexible and the dosing regimen will be dependent on the outcome of Periods 1 to 3. In Periods 4 to 6, there will be the option to optimise the MR release duration and evaluate the impact of a high-fat meal on one or more

already studied MR formulations. In addition, the impact of food (standard breakfast or administration 30 or 60 minutes before a standard breakfast) on selected MR prototype coated tablet formulations may also be evaluated in Period 5 or 6, as applicable. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 3 which shows no clinically significant food effect with a high-fat meal in Period 4. There will be interim decisions after Periods 3, 4 and 5, where appropriate, to determine the formulation and prandial status to be investigated in the next period. Following the final period of Part A, there will be an interim review to determine whether to proceed with optional Part B, and if so, the formulations and tablet strengths to be investigated in Part B.

Optional Part B of the study is an open-label, non-randomised up to 7-period fixed sequence study design to evaluate the selected MR prototype coated formulation(s) at different tablet strengths or as multiple unit doses and with or without apertures in the tablet coatings. Up to 4 different MR prototype coated tablet formulations may be selected for investigation in Part B. These will be selected from Part A and ongoing interim reviews in Part B; the selected formulations may be adjusted during interim reviews during Part B. The tablet strengths and number of dosing units selected in Part B will be based on the exposure of GSK2982772 achieved in an ongoing high dose pharmacokinetic study in which doses of the IR tablet up to 240 mg TID are being administered, and the bioavailability of the selected MR prototype coated tablet formulations relative to the IR tablet (from Part A). Up to 4 different dose levels (as different tablet strengths or multiple unit doses) may be administered in Part B. The proposed dose levels are 120 mg, 480 mg, 960 mg and 1200 mg but these may be adjusted following review of the data from Part A or following the interim reviews during Part B, as appropriate. In Part B, administration of the MR prototype coated tablet formulations will either be in the fed or fasted state, or administered 30 or 60 minutes before a standard or high-fat (Period 7 only) breakfast/evening meal (Period 7 only), which will be based on emerging PK data. There will be an interim review following each of Periods 1 to 5 of Part B to select the dose level, formulation and prandial status, as appropriate, for each subsequent period. An interim data review after Part B Period 6 will determine if optional Period 7 is required and the dose level, dosing time (morning or evening), formulation and prandial status for that period.

Number of Participants:

It is planned to enrol up to 16 participants into each part of the study to allow for sufficient data in at least 12 evaluable participants. For Part A, an evaluable participant will have received the IR tablet formulation (reference) and at least one of the MR formulations and will have completed the planned safety and PK assessments up to 24 hours after dosing. For the food effect assessment, an evaluable subject will have received the chosen MR formulation in the fasted state and the relevant prandial state and will have completed the planned safety and PK assessments up to 48 hours after dosing. For Part B, an evaluable participant will have completed the planned safety and PK assessments up to 48 hours after dosing with at least one MR prototype coated tablet formulation.

Treatment Groups and Duration:

In Part A, each participant will be enrolled in the study for approximately 10 to 12 weeks, dependent on screening and washout duration between periods. Participation will include a screening evaluation within 28 days of study treatment administration and up to 6 separate inpatient periods. Subjects will be admitted to the clinic in the morning of the day before dosing (i.e., Day -1) of each inpatient period. Each inpatient period for the MR regimens (Periods 1 and 3 to 6) will consist of 4 days and 3 nights, and the inpatient period for the IR tablet (Period 2) will consist of 3 days and 2 nights. There will be a minimum washout of 7 days between doses, and a follow-up visit will occur 7 to 9 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period.

In Part B, each participant will be enrolled in the study for approximately 10 to 14 weeks. Participation will include a screening evaluation within 28 days of study treatment administration and up to 7 separate periods. Participants will be admitted to the clinic in the morning of the day before dosing (i.e., Day -1) of each inpatient period. Each inpatient period will consist of a 4-day, 3-night inpatient period with a minimum of 7 days washout between doses. A follow-up visit will occur 7 to 9 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period.

2. SCHEDULE OF ACTIVITIES (SOA)

The schedules of activities for each part are presented in Table 1, and the time points for the pharmacokinetic (PK) blood sample collection in each part are presented in Table 2.

The timing and number of planned study assessments, including safety or PK 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.

Any changes in the timing or addition of time points for any planned study assessments as a result of emerging PK data must be documented and approved by the relevant study team member and then archived in the sponsor and site study files. The competent authority (CA) and ethics committee (EC) will be informed of any safety issues that

constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

PK samples should take priority over other procedures scheduled at the same time point. As guidance, the preferred order of assessments is:

ECGs	→	Vital Signs	→	PK blood sampling (nominal time)	→	Other assessments e.g. physical exams,

Electrocardiograms (ECGs) should be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, e.g., physical examinations etc, will be performed within the required time windows. All safety assessments will be timed and performed relative to the start of dosing.

Table 1 Schedule of Activities for Parts A and B

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 and in Part B only, 7 Day				Follow-up Visit (7 to 9 days post last dose)	Notes
		–1	1	2	3		
Informed consent	X						
Inclusion and exclusion criteria[1]	X						1. Recheck clinical status before 1st dose of study medication.
Demography	X						
Full physical examination including height and weight	X						
Brief physical examination		X		X[2]	X[2]	X	2. Discharge (48 h post-dose for Part B, and Treatment Periods 1, 3, 4, 5 and 6 for Part A; 24 h post-dose for Part A Treatment Period 2 only)
Medical history (includes substance usage)[3]	X						3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X						
Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of non-childbearing potential only)	X						
Serum pregnancy test (WOCBP)	X					X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 and in Part B only, 7 Day				Follow-up Visit (7 to 9 days post last dose)	Notes
		–1	1	2	3		
Urine pregnancy test (WOCBP)		X		X[4]	X[4]		4. Discharge (48 h post-dose for Part B, and Treatment Periods 1, 3, 4, 5 and 6 for Part A; 24 h post-dose for Part A Treatment Period 2 only)
Human Immunodeficiency Virus (HIV), Hepatitis B and C screening[5]	X						5. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Tuberculosis (TB) Test	X						
Urine drug screen	X	X					
Alcohol breath test	X	X					
Carbon monoxide breath test	X	X					
Laboratory assessments (haematology, clinical chemistry and urinalysis)	X	X[6]		X[7]		X	6. Results must be available prior to dosing on Day 1 7. 24 h post-dose Allowable windows in Section 9.4.4
Glomerular filtration rate	X						
C-reactive protein (CRP)	X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 and in Part B only, 7 Day				Follow-up Visit (7 to 9 days post last dose)	Notes
		–1	1	2	3		
12-lead ECG	X[8]	X	X[9]	X[10]		X	8. In triplicate 9. Pre-dose and 2 and 12 h post-dose 10. 24 h post-dose Allowable windows in Section 9.4.3
Vital signs	X	X	X[11]	X[12, 13]	X[13]	X	11. Pre-dose and 2 and 12 h post-dose 12. 24 h post-dose Allowable windows in Section 9.4.2 13. Discharge (48 h post-dose for Part B, and Treatment Periods 1, 3, 4, 5 and 6 for Part A; 24 h post-dose for Part A Treatment Period 2 only)
Genetics blood sample collection (optional)			X[14]				14. A blood sample is collected at the Day 1 visit, after the participant has been randomised and provided informed consent for genetic research. If the sample is not collected on Day 1, it can be collected at any time during the study after randomization. Subjects that decline to provide a sample will still be eligible for this study

Procedure	**Screening (up to 28 days before Day 1)**	**Treatment Period 1, 2, 3, 4, 5, 6 and in Part B only, 7 Day**				**Follow-up Visit (7 to 9 days post last dose)**	**Notes**
		–1	**1**	**2**	**3**		
Study treatment			X[15]				15. Administration of IMP in Part B Period 7 may be in the morning or evening of Day 1. See Section 5.1.3 for more details.
AE review		←==========			==========→		
Serious AE (SAE) review	X	←==========			==========→		
Concomitant medication review		←==========			==========→		
PK blood sample collection			X[16]	X[16]	X[16]		16. Time points in Table 2

Table 2 Pharmacokinetic Blood Sample Collection Times – Parts A and B

	Treatment Periods 1, 3, 4, 5 and 6 (MR Formulations) for Part A and Part B (Treatment Periods 1 to 7[a])																		
Time	**Pre-dose**	**0 h**	**2 h**	**4 h**	**6 h**	**8 h**	**10 h**	**12 h**	**14 h**	**16 h**	**18 h**	**20 h**	**22 h**	**24 h**	**26 h**	**28 h**	**30 h**	**32 h**	**36 h**	**48 h**
Dosing		X																		
PK sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Part A: Treatment Period 2 (IR Formulation)															
Time	**Pre-dose**	**0 h**	**0.33 h**	**0.66 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**8 h**	**10 h**	**12 h**	**24 h**
Dosing		X													
PK sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X

[a] The time of dosing in Part B Period 7 (morning or evening) will be decided during the interim data review after Part B, Period 6.

3. INTRODUCTION

GSK2982772 is a first-in-class, highly selective, receptor-interacting protein-1 (RIP1) kinase inhibitor being developed for the treatment of inflammatory bowel disease, plaque psoriasis (PsO), rheumatoid arthritis (RA) and other disease conditions.

3.1. 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 tumour necrosis factor (TNF) family cytokines, ligands for toll like receptor (TLR)3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis [Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008; Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and Nuclear factor-kappaB-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, such as ulcerative colitis, chronic PsO and RA, through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK2982772 is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2014N204126_03].

3.2. Study Rationale

Pharmacokinetic data from the first time in human (FTIH) study for GSK2982772 (200975) [GlaxoSmithKline Document Number 2014N204126_03] showed that the half-life of GSK2982772 was short (~2 to 3 hours). As a result, twice daily (BID) and three times daily (TID) dosing regimens are being evaluated in three ongoing proof of mechanism studies. A once daily (QD) formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. Pharmacokinetic data from a modified release (MR) formulation study (205017) showed that a QD formulation was feasible; however, the MR formulation (minitabs in capsules) was susceptible to a food effect and a MR monolithic matrix tablet formulation may be mechanistically susceptible to a food effect as well. This study will evaluate the feasibility of developing an MR prototype coated tablet formulation using a combination of a controlled release polymer matrix and

controlled-release coating. The MR tablet coating used in Part A and the initial periods of Part B will have an aperture drilled into the enteric coating of either side of the tablet. This allows some drug release to commence in the stomach whilst providing controlled release throughout the GI tract. This MR tablet coating has been used in other formulations (e.g. Lamictal XR) and in vivo has shown robustness against food effects. The hypromellose (HPMC) polymer has been shown to be effective in achieving a controlled delay to the drug release rate and thus lowering maximum observed concentration (C_{max}) and increasing the concentration at 24 h post-dose (C_{24h}) of the product. However, it is believed that the digestive mechanical action that the dosage form is exposed to in the fed stomach, and/or the longer stomach retention time when dosed in the fasted state, causes an increase in the rate of drug release. Application of an enteric coating with apertures will control the release rate when in the stomach. The MR prototype coated tablet formulations have a matrix core containing hypromellose polymers. The MR prototype coated tablet formulations will be optimised within a one-dimensional design space where release rate from the tablet will be adjusted by varying the polymer ratio in the tablet core. In Part B only, a new IMP will be manufactured to allow comparison of the tablet coating either with apertures (i.e., drilled) or without apertures (i.e., full coat/non-drilled).

The Clinical Trial Authorisation application for this study describes a flexible protocol design using the concept of formulation design space to allow decision-making in response to interim PK observations. The principles of a flexible protocol were discussed and agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) at a Scientific Advice Meeting between the MHRA and Quotient Sciences (formerly Pharmaceutical Profiles).

Based upon the concept of formulation design space, specific Investigational Medicinal Products (IMPs) are not detailed within the Investigational Medicinal Product Dossier but rather a defined range of formulation inputs and corresponding performance outputs are described and justified based on in vitro studies.

3.3. Benefit/Risk Assessment

As of 10 November 2018, approximately 296 participants have been enrolled in 8 clinical studies with GSK2982772. In completed Study 200975, GSK2982772 was administered up to 120 mg BID for 14 days (total daily dose 240 mg). A total of 67 participants received GSK2982772 and 26 participants received placebo (including crossover) in that study, of whom 31 participants received a single dose of GSK2982772. No safety concerns were identified and no SAEs, including deaths, were reported in this study.

In ongoing Phase 1 studies (high dose PK Study [205184] and modified release formulation Study [205017]), a total of approximately 47 and 45 participants have been randomised to single doses of GSK2982772 up to 720 mg/day and repeat doses up to 300 mg/day for 3 days, respectively. In this ongoing Phase 1 study 209261, approximately 17 healthy subjects have been exposed to GSK2982772 as of 10 Nov 2018.

In the ongoing GSK2982772 study 205184 (A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects), a subject experienced an asymptomatic non-serious adverse event of elevated ALT [7.5 × upper limit of normal (ULN)] and AST (4.5 × ULN) on study Day 15, one day after completing a 14 day treatment of GSK2982772 120 mg orally three times a day. Due to the absence of another plausible explanation, the event was considered likely related to study drug and was severe in intensity. Bilirubin, prothrombin time, and work-up were all within normal limits and both ALT and AST returned to normal within 4 weeks. Confounders included the following:

1. Subject received 1 g dose of paracetamol on study Day 13 for headache.

2. Subject had a history of mild aminotransferase elevation (1.7 and 1.3 × ULN for ALT and AST, respectively) in another healthy volunteer study while receiving an investigational monoclonal antibody.

3. Subject's AST slightly increased (1.75 × ULN) during the follow-up period after initially declining to normal. Creatine phosphokinase (CPK) was also elevated at that time and this elevation could be associated with physical activity.

The benefit/ risk profile is considered unchanged by this single, reversible and monitorable event.

In ongoing Study 205017 (A three-part, non-randomised, open label Phase 1 Study 205017 assessing the PK of GSK2982772 modified release (MR) formulations relative to an immediate release (IR) reference formulation (Part A), the PK of escalating, repeat doses of a selected MR prototype (Part B), and the PK of GSK2982772 following administration of MR formulation in the fed and fasted state (Part C)), a completed suicide was reported 29 days after the subject received a single dose of GSK2982772. This subject had a prior undisclosed suicide attempt and the event was determined by the Investigator to be unlikely related to study drug. Given the short half-life of GSK2982772, there is no temporal relationship to support a causal association.

In the Phase 2a studies in PsO (Study 203167) and RA (Study 203168) and in the ongoing Ulcerative Colitis (Study 202152), approximately 107 participants (47 in the PsO study, 33 in the RA study) have been randomised/exposed to GSK2982772 60 mg BID or 60 mg TID. In Study 203167, there was a death of a 19-year-old male participant due to an accidental overdose with recreational drug 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

There is currently limited information available about the relationship of adverse events (AEs) to administration of GSK2982772 in human subjects. Therefore, all serious adverse events (SAEs) are considered unexpected. Any SAE deemed related to the IMP will be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR), in compliance with local health authority safety reporting requirements (see Appendix 7).

There was no maternal or developmental toxicity at doses ≤200 mg/kg/day in rats and no developmental toxicity was evident at doses up to 300 mg/kg/day in rabbits (area under concentration vs time curve [AUC] of 1270 µg.h/mL and C_{max} of 153 µg/mL). Non-clinical studies show no evidence of genotoxicity or teratogenicity.

The compound must not be administered to pregnant women or nursing mothers. Women of childbearing potential must use highly effective methods of contraception (<1% failure rate; Appendix 5) for 30 days prior to exposure to GSK2982772 until the follow-up visit for the final dosing period (7-9 days after the last dose).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK2982772 may be found in the Investigator's Brochure.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2982772		
Central Nervous System (CNS) effects	**Non-clinical data**: In the 4-week Good Laboratory Practice (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 no observed adverse effect level (NOAEL) for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. In the 39-week GLP toxicology study, there were no CNS findings observed in monkeys administered 6, 20 or 60 mg/kg/day. The NOAEL for this study was determined at 60 mg/kg/day. **Clinical data**: A FTIH study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date. See Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_03]. No drug-associated CNS AEs were identified and no SAEs were reported. In the Phase 2a psoriasis study (203167), there was one	**Subject Selection**: • Subjects with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening. **Subject Monitoring**: • Subjects will be monitored for standard CNS-related AEs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	SAE of death via accidental overdose of Ecstasy/MDMA in a subject receiving GSK2982772 60 mg BID. There was no evidence reported to suggest that this event was a suicide.	
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. **Clinical data**: In the FTiH study, no SAEs were reported. One subject in the FTiH study was diagnosed with herpes zoster 42 days after receiving GSK2982772 80 mg (Treatment Period 2). The blinded investigator considered the AE to be potentially drug-related. One subject from the PsO study experienced an AE of herpes zoster on Study Day 9 (GSK2982772 60 mg BID). The blinded investigator considered the AE to be of moderate severity and not related to study drug.	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, HIV, Hepatitis B and C, and excluded from the study if positive. **Subject Monitoring**: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 8.1.3).
Vaccinations	No preclinical data. There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (e.g., risk of theoretical

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
Respiratory	**Non-clinical data**: In the single dose Safety Cardiovascular (CV) and Respiratory Study in monkeys, a decrease in minute volume and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (minute volume) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See Investigator's Brochure for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_03]. **Clinical data**: In the FTIH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal carbon dioxide (CO_2), oxygen saturation and nocturnal respiratory rate monitoring was performed. No SAEs were reported, and no drug-associated respiratory-related AEs were identified.	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related AEs. • Vital signs will be monitored during study visits.
Suicidality	GSK2982772 is considered to be a CNS-active drug based upon pre-clinical studies. **Clinical data**: In the FTIH study, there have been some reports of lethargy, abnormal dreams, and depressed mood.	**Subject Selection**: • Subjects with a current history of suicidal ideation and behaviour (SIB) or a history of attempted suicide will be excluded from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In the Phase 2a psoriasis study, one subject reported suicidal ideation at Day 43 via the Columbia Suicide Severity Rating Scale. Per the investigator, this subject was questioned at the next visit and reported that he had had these thoughts on and off prior to joining the study and did not plan to take action on these feelings. The investigator kept the subject on study. In the open-label modified release formulation study (205017), a completed suicide was reported 29 days after the subject received a single dose of GSK2982772. This subject had a prior undisclosed suicide attempt and the event was determined by the Investigator to be unlikely related to study drug. Given the short half-life of GSK2982772, there is no temporal relationship to support a causal association.	**Subject Monitoring:** • Subjects receiving multiple doses should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour.
Reproductive toxicity	**Non-clinical data:** There was no maternal or developmental toxicity at doses ≤ 200 mg/kg/day in rats and no developmental toxicity was evident at doses up to 300 mg/kg/day in rabbits (AUC of 1270 µg.h/mL and C_{max} of 153 µg/mL). When GSK2982772 was given to F0 female rats from gestation day (GD) 6 through lactation day (LD) 21, there was no maternal toxicity observed up to a dose of 300 mg/kg/day, the highest dose tested. There were no effects on F1 viability up to 300 mg/kg/day, or F1 growth and development up to 100 mg/kg/day. At 300 mg/kg/day, mean pup weight was lower than the control from post-natal day (PND) 1 through PND 21. In female rats, GSK2982772 was given for 15 days prior to cohabitation, through cohabitation and on GD 0 to 6. There was decreased body weight gain and food	**Subject Selection**: • Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for 30 days before first administration of study drug until study completion (Appendix 5). • Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	consumption prior to mating at 400 mg/kg/day and during gestation at >200 mg/kg/day. At the dose level of 400 mg/kg/day, there were effects on reproductive performance (decreased mean numbers of corpora lutea, implantations and mean live litter size and increased post-implantation loss). The NOAEL for female fertility and early embryonic development in rats was considered to be 200 mg/kg/day. In male rats, there were no effects on mating, fertility and organ weights, and no male-mediated foetal developmental toxicity following administration of 10, 60 or 200 mg/kg/day for 44-45 days. Therefore, the NOAEL for reproductive performance and for male-mediated developmental toxicity is 200 mg/kg/day. The mutagenic and clastogenic potential of GSK2982772 has been assessed using in vitro tests in bacteria and cultured mammalian cells and also in an in vivo rodent bone marrow micronucleus assessment to test for induction of structural chromosomal damage and/or aneuploidy. Appropriate vehicle and positive controls were included in each test. In addition, an assessment of the route of synthesis for GSK2982772 has been conducted to determine if there are any impurities which are known or suspected deoxyribonucleic acid (DNA)-reactive mutagens are likely to be present in the final drug substance. Non-clinical studies show no evidence of genotoxicity or teratogenicity.	elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and	**Subject Selection:** • No concomitant medications will be permitted in this study with the exception of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	OAT3 substrates were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of a drug interaction with OAT3 substrates. There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772. GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772. See Section 4.3.6 of the GSK2982772 Investigators Brochure [GlaxoSmithKline Document Number 2014N204126_03].	paracetamol/acetaminophen, hormonal contraception, hormone replacement therapy and other treatments required for AEs. **Subject Monitoring:** ● Caution is advised when dosing GSK292772 with CYP3A4 NTI substrates, OAT3 substrates or Pgp inhibitors.
Study Procedures		
Cannulation	During cannulation, more than one attempt may be needed to insert the cannula in a vein of a participant and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.	• A vein assessment will be conducted at screening to ensure only volunteers with veins suitable for multiple venepuncture and cannulation are enrolled. Cannulation and venepuncture will only be performed by staff who are trained in these procedures.
Electrocardiograms	Electrocardiogram stickers on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove.	• Participants will be closely monitored to ensure any local irritation does not persist.

3.3.2. Benefit Assessment

There is no intended direct health benefit to the participants in this study. The benefit to participants include contributing to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to healthy participants participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded to patients with inflammatory conditions such as ulcerative colitis, PsO and RA.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each MR prototype coated tablet formulation (240 mg) compared to the IR formulation (240 mg) (Part A)	• GSK2982772 area under the curve from time zero to infinity ($AUC_{(0\text{-}inf)}$), area under the curve from time zero to the last measurable concentration ($AUC_{(0\text{-}t)}$), area under the curve from time zero to 24 hours ($AUC_{(0\text{-}24)}$), maximum observed concentration (C_{max}), concentration at 24 hours post-dose (C_{24h}), time to C_{max} (T_{max}), terminal half-life ($t_{1/2}$)
• To assess the impact of a high-fat breakfast on the PK of GSK2982772 following single dose administration of one or more selected MR prototype coated tablet formulations (240 mg) (Part A or Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max}, C_{24h}, and $t_{1/2}$, relative bioavailability ($FreI_{FE}$), relative bioavailability ($FreI_{Formulation}$), based on AUC and C_{max}
Secondary	
• To assess the safety and tolerability of single doses of GSK2982772 (Part A)	• AEs • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead electrocardiogram (ECG) monitoring

Objective	Endpoint
• To determine the bioavailability of GSK2982772 MR prototype coated tablet formulations relative to the IR reference, as appropriate (Part A)	• Relative bioavailability ($Frel_{formulation}$) based on AUC and C_{max}
Exploratory	
• To assess the safety and tolerability of single doses of GSK2982772 (Optional Part B)	• AEs • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead electrocardiogram (ECG) monitoring

Objective	Endpoint
• To evaluate the PK profile of alternative tablet strengths of selected GSK2982772 MR prototype coated tablet formulations (Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, C_{max}, C_{24h}, $t_{1/2}$, AUC/Dose and C_{max}/Dose
• To evaluate the impact of dosing 2 or more MR prototype coated tablets on the PK profile of GSK2982772 (Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$ or $AUC_{(0\text{-}24)}$, C_{max}, T_{max} and $t_{1/2}$
• To determine if there are any dose dependent changes in the absorption of GSK2982772 following single dose administration selected GSK2982772 MR prototype coated tablet formulations (Optional Part B)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, C_{max}, C_{24h} and T_{max}
• To assess the impact of a standard breakfast on the PK of GSK2982772 following single dose administration of one or more selected MR prototype coated tablet formulations (240 mg) (Part A - optional)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $t_{1/2}$, relative bioavailability ($Frel_{FE}$), relative bioavailability ($Frel_{Formulation}$), based on AUC and C_{max}
• To assess the impact of a delayed meal on the PK of GSK2982772 following single dose administration of one or more selected MR prototype coated tablet formulations (240 mg) (Part A - optional)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $t_{1/2}$, relative bioavailability ($Frel_{FE}$), relative bioavailability ($Frel_{Formulation}$), based on AUC and C_{max}
• To assess the impact of evening dosing (Optional Part B, Period 7 only) on the PK of GSK2982772 following single dose administration selected GSK2982772 MR prototype coated tablet formulations.	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $t_{1/2}$, relative bioavailability (Frel (time effect), based on AUC and C_{max}

5. STUDY DESIGN

5.1. Overall Design

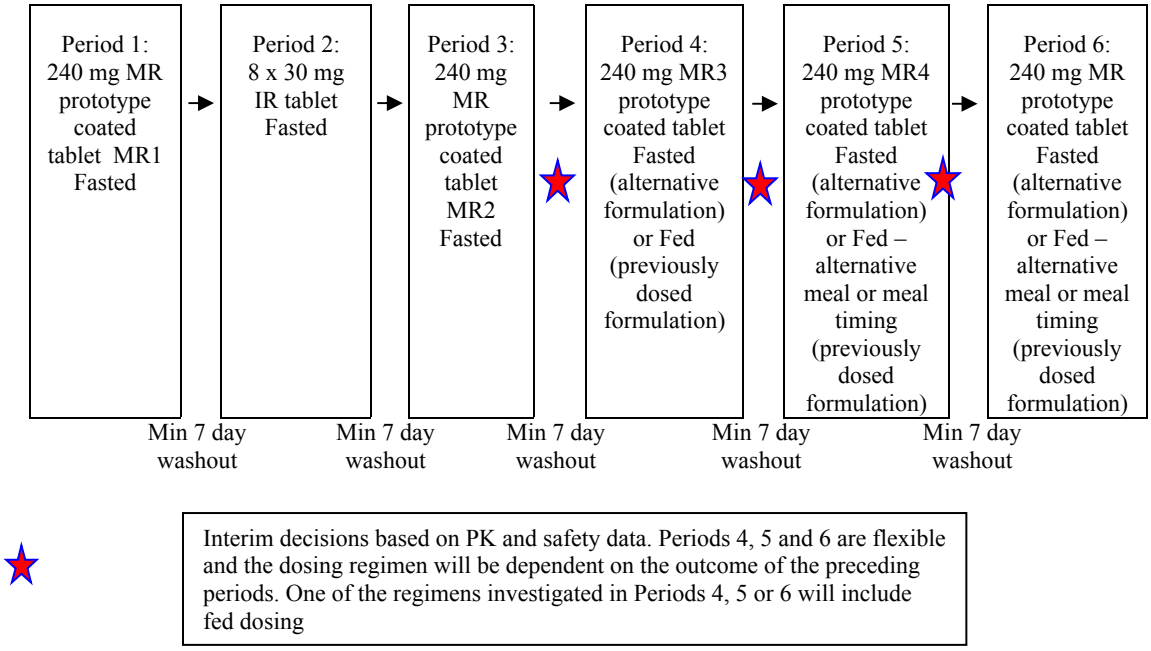
This is an open label, non-randomised single centre, two part, single dose study in healthy male and female participants to assess MR prototype coated tablet formulations of GSK2982772. The impact of food (high-fat breakfast) on the rate and extent of absorption will be evaluated for suitable MR prototype coated tablet formulations, and an assessment of alternative tablet strengths, dosing of multiple dose units and presence/absence of apertures in the tablet may also be performed. An assessment of a standard or high-fat breakfast/evening meal or study drug administration 30 or 60 minutes before a standard or high-fat breakfast or evening meal (Part B, Period 7 only) may also be included. The single dose may be given in the morning or evening (Part B, Period 7 only).

5.1.1. Part A

Part A of the study is a non-randomised up to 6 period, 6-way fixed sequence design in which up to 4 MR tablet prototype coated formulations may be evaluated following single dose administration in the fasted state (240 mg) (Figure 1). Periods 1, 2 and 3 will evaluate MR1 (similar in vitro dissolution to the slowest minitab MR formulation from study 205017), IR Tablet (240 mg) and MR2 (slower in vitro dissolution than MR1) respectively. Periods 4, 5 and 6 will be flexible and the dosing regimen will be dependent on the outcome of Periods 1 to 3. In Periods 4 to 6, there will be the option to optimise the MR release duration and evaluate the impact of a high-fat meal of one or more already studied MR formulations. In addition, the impact of food (standard breakfast or administration 30 or 60 minutes before a standard breakfast) on selected MR prototype coated tablet formulations may also be evaluated in Period 5 or 6, as applicable. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 3 which shows no clinically significant food effect with a high-fat meal in Period 4. There will be interim decisions after Periods 3, 4 and 5, where appropriate, to determine the formulations and prandial status to be investigated in the next period. Following the final period of Part A, there will be an interim review to determine whether to proceed with optional Part B, and if so, the formulations and tablet strengths to be investigated in Part B.

Each inpatient period for the MR regimens (Periods 1, 3, 4 to 6) will consist of 4 days and 3 nights, and the inpatient period for the IR tablet (Period 2) will consist of 3 days and 2 nights. There will be a minimum washout of 7 days between doses, and a follow-up visit will occur at 7 to 9 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period.

Figure 1 Part A Study Design – Formulation Optimisation and Food Effect



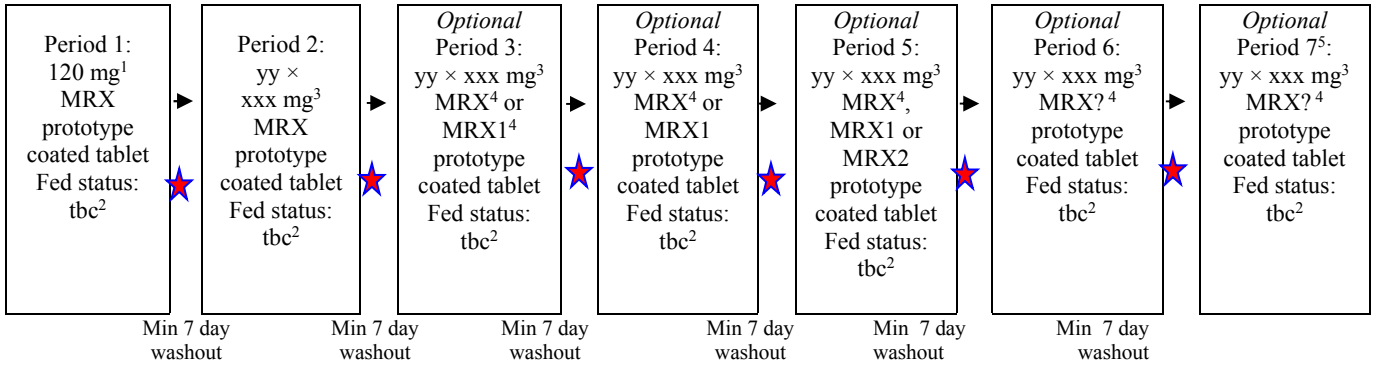
5.1.2. Part B

Optional Part B of the study is an open-label, non-randomised up to 7-period fixed sequence study design to evaluate the selected MR prototype coated tablet formulation(s) at different tablet strengths or as multiple unit doses and with or without apertures in the tablet coatings (Figure 2). Up to 4 different MR prototype coated tablet formulations may be selected for investigation in Part B. These will be selected from Part A and ongoing interim reviews in Part B; the selected formulations may be adjusted during interim reviews in Part B. The tablet strengths and the number of dosing units selected in Part B will be based on the exposure of GSK2982772 achieved in an ongoing high dose PK study in which doses of the IR tablet up to 240 mg TID are being administered, and the bioavailability of the selected MR prototype coated tablet formulations relative to the IR tablet (from Part A). Up to 4 different dose levels (as different tablet strengths or multiple unit doses) may be administered in Part B. The proposed dose levels are 120 mg, 480 mg, 960 mg and 1200 mg but these may be adjusted following review of the data from Part A or following the interim reviews during Part B, as appropriate. In Part B, administration of the MR prototype coated tablet formulations will either be in the fed or fasted state, or administered 30 or 60 minutes before a standard or high-fat (Period 7 only) breakfast/evening meal (Period 7 only), which will be based on emerging PK data. There will be an interim review following each of Periods 1 to 5 of Part B to select the dose level, formulation and prandial status, as appropriate, for each subsequent period. An interim data review after Part B Period 6 will determine if optional Period 7 is required and the dose level, dosing time (morning or evening), formulation and prandial status for that period.

Participants will be admitted to the clinic in the morning of the day before dosing (i.e., Day -1) of each inpatient period. Each inpatient period will consist of a 4-day, 3-night

inpatient period with a minimum of 7 days washout between doses. A follow-up visit will occur at 7 to 9 days after the last study treatment.

Figure 2 Part B Study Design – Tablet Strength



Interim decisions based on PK and safety data. Periods 2 to 7 are flexible and the dosing regimen will be dependent on the outcome of the preceding periods.

[1] Proposed dose levels that may be adjusted following review of the data from Part A

[2] Administration of the MR prototype coated tablet formulations will either be in the fed or fasted state or administered 30 or 60 minutes before a standard or high-fat (Period 7 only) breakfast/evening meal (Period 7 only).

[3] Different tablet unit strengths may be used to achieve the required dose level

[4] Tablet may be manufactured with or without apertures (i.e., drilled or non-drilled). Tablets without apertures will be manufactured based on a formulation which has already been dosed.

[5] Dosing will either be in the morning or evening of Day 1.

5.1.3. Criteria for Interim Decisions

In Part A there will be an interim review following completion of Period 3, Period 4 and Period 5, where appropriate, to decide whether to dose a different MR prototype coated tablet formulation (created by adjusting the percentage polymer content in the core or the polymer ratios) or whether to dose one of the previously dosed formulation in the fed state (high-fat breakfast). Once the impact of a high-fat meal on a selected MR has been studied, the subsequent periods may be dosed in the fasted or fed state (a high-fat breakfast or standard breakfast) or dosing 30 or 60 minutes before a standard breakfast. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 3 which shows no clinically significant food effect with a high-fat meal in Period 4. Following the final period of Part A, there will be an interim review to determine whether to proceed with optional Part B, and if so, the formulations and tablet strengths to be investigated in Part B. The decision to progress to Part B will be based upon identifying a formulation from Part A that has an appropriate exposure profile and does not show a clinically significant food effect with 1 or more of the food states described above. There will be an interim review following each of Periods 1 to 5 of Part B to select the dose level, formulation and prandial status, as appropriate, for each subsequent period. An interim data review after Part B Period 6 will determine if optional Period 7 is required and the dose level, dosing time (morning or evening), formulation and prandial status for that period.

The highest dose level may be adjusted based on observed relative bioavailability of the MR tablet but will be planned that the mean $AUC_{(0-24)}$ and mean C_{max} will not exceed the GSK2982772 systemic exposure associated with the single day administration of 240 mg IR TID (i.e., mean $AUC_{(0-24)}$ of 45.0 µg.h/mL and mean C_{max} of 4.3 µg/mL). These exposures are below those achieved at the monkey and rat no observed adverse effect levels in the 13-week toxicology studies.

Interim decisions will only be made after a complete review of all relevant data collected from the previous dose group. Data should be available from a minimum of 12 participants who have completed the planned safety and PK assessments up to 24 hours after dosing, or 48 hours after dosing for the food effect assessment and for Part B; if full data, as described below, are not available for 12 participants, the PI, scientific lead and sponsor will take a decision as to whether the data available are sufficient to support the formulation selection decision. An evaluable participant must also have received the relevant test and reference formulations for the comparisons of interest e.g., an MR formulation and the IR reference and/or the selected MR formulation in both the fed and fasted states. If data in fewer than 12 participants are used in the decision process, replacement participants will not be dosed with previous regimens to increase the number of participants in the completed regimen.

The following data will be provided to the sponsor by Quotient Sciences:

- AEs, vital signs, ECGs, safety laboratory data and physical examinations.
- Plasma concentrations of GSK2982772.

- PK parameter estimates GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, T_{lag} ,T_{max}, C_{max}, C_{24h}, (C_{12h} for IR only) $t_{1/2}$, Frel based on AUC and C_{max} for test vs reference formulations and fed vs fasted, where relevant (Part A).

- PK parameter estimates GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, T_{max}, $C_{max,}$ $C_{24h,}$ $t_{1/2}$ (Part B).

- Protocol deviations will be reviewed to ensure they have had no significant impact on the above data

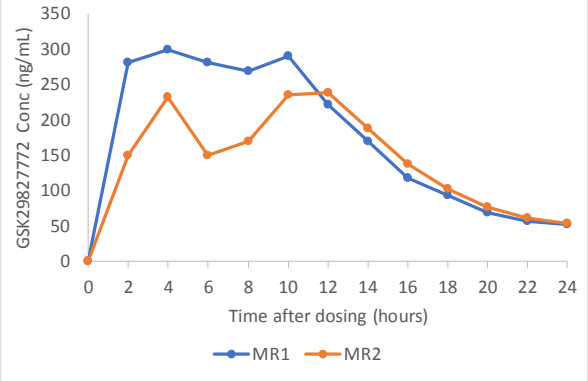
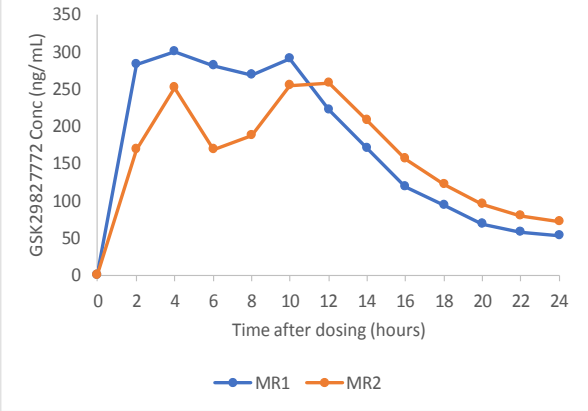
The decision on formulation, tablet strength, dose level, dosing time (Part B Period 7 only) and prandial state selection or stopping the study will be made by the Quotient study team (i.e., PI, scientific lead and pharmacokineticist) and sponsor study team (as a minimum the sponsor's medical monitor, Clinical Pharmacokinetics Modelling and Simulation [CPMS] and Global Clinical Safety and Pharmacovigilance [GCSP]). The decision will be documented and signed by the PI as per Quotient Sciences current standard operating procedure (SOP). Evidence of the decision will be retained in the Investigator Site File (ISF) and GlaxoSmithKline (GSK) Trial Master File.

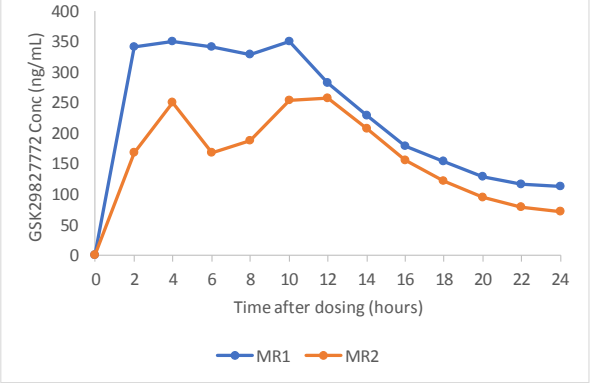
The following decision criteria will be used as a guide to MR formulation selection during the study.

Since the aim of the MR development programme in to provide a QD formulation with as high as possible C_{min}, the decision criteria will be based on this PK parameter. To avoid issues with potential outliers at a single nominal time point (e.g. defining C_{24h} as minimum observed concentration [C_{min}]), the decision criteria will be based on the nominal PK sampling times between 18 and 24 hours. Other PK parameters may also be taken into consideration in the MR formulation selection including, but not limited, to bioavailability relative to IR, ratios of C_{max}:C_{18h}, C_{max}:C_{20h}, C_{max}:C_{22h} and $C_{max:}C_{24h}$ and between subject coefficient of variation (CVb) of C_{18h}, C_{20h}, C_{22h} and C_{24h}. The duration of drug release may also be taken into consideration since shorter drug release durations using weaker polymers may be more susceptible to food effect whereas longer release duration will be more susceptible to PK variability due to inter- and intra-subject differences in gastrointestinal transit time.

Food effect arm/s may be conducted with one or more MR formulations and/or one or more fed states.

N.B. The release rate of MR1 is planned to be similar to the slowest release minitab in study 205017 (~12h for 80% release) and the release rate of MR2 will be the slowest available within the design space.

Decision Criteria for Part 1: Period 4		
Criteria/ Action	**Illustration**	**Rationale**
If in the majority of nominal PK sampling time points between 18 and 24 hours, the ratio of the geometric mean GSK2982772 concentrations for MR2:MR1 is between 0.9 and 1.1, then evaluate a release duration faster than MR1		No benefit of extending drug release beyond 12 hours
If in the majority of nominal PK sampling time points between 18 and 24 hours, the ratio of the geometric mean GSK2982772 concentrations for MR2:MR1 >1.1, then evaluate an intermediate release duration between MR1 and MR2		If MR2 >MR1, the MR2 (with a longer duration of drug release) will be more susceptible to variability in gastrointestinal (GI) transit time therefore want to see if shorter duration of release than MR2 will still provide higher concentrations between 18 and 24 hours than MR1

If in the majority of nominal PK sampling time points between 18 and 24 hours, the ratio of the geometric mean GSK2982772 concentrations for MR2:MR1 <0.9 then evaluate a release duration faster than MR1		Want to see if shorter duration of release than MR1 will provide even higher C_{min} than MR1

Decision Criteria for Part 1: Period 5

If an intermediate release rate (MR3) is evaluated in Period 4, then a 2nd intermediate release rate (MR4) between MR3 and either MR1 or MR2 may be evaluated using the same criteria as in Period 4. If the criteria for evaluating an intermediate release rate in Period 5 are not met, then either MR1, MR2 or MR3 will be administered with a high-fat meal in Period 5.

If a faster release rate than MR1 is evaluated in Period 4, then an even faster release rate or an interim release rate between MR3 and MR1 or MR2 may be evaluated based on the same criteria as Period 4. If the criteria for evaluating an even faster release rate on an intermediate release rate in Period 5 are not met, then either MR1 or MR3 will be administered with a high-fat meal in Period 5.

Decision on which MR Formulation to be used for assessment of High-Fat Meal: Periods 4, 5 and/or 6

The MR formulation to be selected for the food effect arm will ideally have the highest GSK2982772 concentrations in the majority of timepoints between C_{18h} and C_{24h} along with the lowest CV_b.

Decision on which MR Formulation to be taken to Part 2

The duration of release for the 120 mg and 480 mg MRX formulations in Periods 1 and 2 will have a similar release rate duration as the optimal MRX formulation from Part A, where optimal is defined in the same way as for the food effect arm (e.g. the highest GSK2982772 concentrations in the majority of timepoints between C_{18h} and C_{24h} along with the lowest $CV_{b)}$.

Decision of whether to evaluate 480 mg or 120 mg MR_{Yh} in Part B

If dose normalised C_{min} is ≥10% different compared to the 240 mg dose normalised C_{min},

then the MR release duration may be adjusted in Period 3 and/or Period 4.

5.2. Number of Participants

It is planned to enrol up to 16 participants into each part of the study to allow for sufficient data in at least 12 evaluable participants. For Part A, an evaluable participant will have received the IR tablet formulation (reference) and at least one of the MR formulations and will have completed the planned safety and PK assessments up to 24 hours after dosing. For the food effect assessment, an evaluable subject will have received the chosen MR formulation in the fasted state and the relevant prandial state and will have completed the planned safety and PK assessments up to 48 hours after dosing. For Part B, an evaluable participant will have completed the planned safety and PK assessments up to 48 hours after dosing with at least one MR prototype coated tablet formulation.

Participants withdrawn due to an IMP-related AE that is at least moderate in severity or termination of the study will not be replaced. If participants prematurely discontinue the study for other reasons, additional replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator.

Up to 4 replacement participants may be enrolled in each part of the study. The maximum number of participants that may be dosed in each part of the study is 20.

Replacement participants enrolled will be dosed with the next planned treatment of the withdrawn participant, and they will not receive any treatment that the withdrawn participant has already received unless required to obtain the minimum number of evaluable participants required for interim decisions, and to obtain data in any other treatment that is required for a valid comparison. Replacement participants will receive the required treatments in the same order as planned for the original participants and the minimum washout period will be respected with regard to the timing of dosing.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA i.e., the follow-up visit.

The definition of the end of the study is defined as the point at which the sponsor determines that any remaining optional groups are not required to meet the objectives of the trial i.e., signed dose decision document. If all optional groups are used, completion of the last follow-up visit will be considered the end of the study.

5.4. Scientific Rationale for Study Design

Previous clinical studies of IR formulations of GSK2982772 resulted in a high peak:trough ratio of GSK2982772. Additionally, the short half-life for GSK2982772 (~2 to 3 hours) necessitates BID or TID dosing of an IR formulation. As a result, MR formulations using a polymer matrix approach with minitablets in capsule and MR tablet

formulations were investigated. The emerging PK data of the MR formulations investigated to date have demonstrated that a QD PK profile can be achieved in the fasted state but the polymer matrix formulation is susceptible to food effects when administered with a high-fat breakfast. The purpose of this study is to evaluate MR prototype coated tablet formulations. The MR prototype coated tablet formulation uses a combination of a controlled-release polymer matrix and controlled-release coating to achieve a modified-release of the drug. The MR tablet coating used in Part A and the initial periods of Part B will have an aperture drilled into the enteric coating of either side of the tablet. This allows some drug release to commence in the stomach whilst providing controlled release throughout the GI tract. This MR tablet coating has been used in other formulations (e.g. Lamictal XR) and in vivo has shown robustness against food effects. The HPMC polymer has been shown to be effective in achieving a controlled delay to the drug release rate and thus lowering C_{max} and increasing the C_{24h} of the product. However, it is believed that the digestive mechanical action that the dosage form is exposed to in the fed stomach, and/or the longer stomach retention time when dosed in the fasted state, causes an increase in the rate of drug release. Application of an enteric coating with apertures will control the release rate when in the stomach. In Part B only, a new IMP will be manufactured to allow comparison of the tablet coating either with apertures (i.e., drilled) or without apertures (i.e., full coat/non-drilled).

Part A of the study is an adaptive crossover study that will optimise the MR prototype coated tablet formulation to provide a formulation suitable for QD dosing and has no clinically significant food effect. The MR prototype coated tablet formulations have a matrix core containing hypromellose polymers. The MR prototype coated tablet formulations will be optimised within a one-dimensional design space where release rate from the tablet will be adjusted by varying the polymer ratio in the tablet core. The polymers will be hypromellose 2208 K3LV (polymer 1) and/or K100LV (polymer 2) and/or K4M (polymer 3). The dose will be fixed at 240 mg, and the in vitro release rate will be targeted such that the tablet core of GSK2982772 MR prototype coated tablet formulation MR1 will have a dissolution profile that is similar to the release rate of the slowest release MR minitab formulation from Study 205017 (approximately 80% in vitro release at 12 hours). GSK2982772 MR prototype coated tablet formulation MR2 will be designed such that the in vitro dissolution is slower than that of MR1, and will be the slowest available within the design space. If neither MR1 nor MR2 provide an optimal profile, further MR prototype coated tablet formulations will be investigated. The impact of food on the pharmacokinetics of GSK2982772 will also be evaluated for the selected formulation(s). After completion of Periods 3, 4 and 5, interim analyses will be conducted to determine the formulation and prandial status to be investigated in the next period. After completion of Part A, an interim analysis will be conducted to identify MR prototype coated tablet formulations for progression into Part B. If none of the MR prototype coated tablet formulations are suitable, then Part B of the study may not be conducted or Part B may be used to continue to optimise the MR prototype coated tablet formulations, which may include varying the tablet coating either with apertures (i.e. drilled) or without apertures (i.e., full coat/non-drilled) by the manufacture of a new IMP.

Optional Part B will assess the pharmacokinetics of alternative tablet strengths (120 mg and 480 mg, or alternative strengths) as allowed by the design space or tablets with apertures (i.e., drilled) or without apertures (i.e., full coat/non-drilled) or multiple dosing

units of the optimum MR formulation selected from Part A. If the in-vivo profile of either or both the 120 mg or 240 mg tablets (or alternative strengths) differs from the optimal profile with the 240 mg, the ratio of the polymers K3LV, K100LV and/or K4M may be adjusted within each of the alternative strengths. In order to assess the effect of the aperture on the in vivo performance of the formulation, a fully coated tablet (i.e., without apertures) may be assessed in Part B, Period 3 onwards. If fully coated tablet(s) are dosed, the core composition will match a previously dosed formulation to allow a valid comparison. To investigate whether the between-subject variability in absorption time observed following administration of 480 mg tablet with a high-fat breakfast (administered in previous periods) can be reduced; a change to the food regimen or time of administration may be explored in Part B, Period 7. Subjects may be dosed in the fasted state or fed state (standard or high-fat breakfast/evening meal) or in the fasted state followed by a delayed standard or high-fat breakfast/evening meal, on the morning or evening of Day 1. Prior to initiation of Part B, a substantial amendment to the investigational medicinal product dossier (IMPD), will be submitted to the MHRA for approval, to include updated information on the selected GSK2982772 MR prototype coated tablet formulations at alternative strengths.

As this is a Phase 1 study, the most relevant population is healthy participants which allows characterisation of safety, tolerability and PK in a homogenous population without potential biases from a patient population. The European Medicines Agency (EMA) recommends including participants aged 18 years and older with normal weight, who are non-smokers, without a history of alcohol or drug abuse. The latter criteria are proposed to avoid interaction on drug metabolism and to avoid non-compliance. Therefore, this study will enrol healthy male and female participants aged between 18 to 65 years of age.

5.5. Dose Justification

In the blinded high dose PK study (205184) in healthy participants, single doses up to 720 mg/day appear to be well-tolerated with no safety concerns identified. No SAEs or deaths have been reported. Repeat dosing with up to 720 mg/day x 14 days is ongoing.

Single doses are to be used in this study since single doses are generally more sensitive than steady-state dosing in assessing rate and extent of release of the drug substance from the drug product into the systemic circulation. In addition, GSK 2982772 has time in-dependent pharmacokinetics as demonstrated with similar single and repeat dose PK profiles following 14 days dosing with GSK2992772 Immediate Release (Study 200975) and following 3 days dose with minitab MR (Study 205017). Single doses are also required for development of in-vitro / in-vivo correlation which may be developed for the DiffCore formulation at a later date".

In Part A, a dose of 240 mg has been selected as this is expected to be safe and well tolerated, and is within the expected dose range that is planned to be taken forward into the Phase 2b dose ranging studies.

In Part B, the selection of the doses will be based on the results from Part A. The highest dose will not be predicted to exceed the GSK2982772 systemic exposure associated with the single day administration of 240 mg TID (i.e., mean $AUC_{(0-24)}$ of 45.0 µg.h/mL and

mean C_{max} of 4.3 µg/mL). These exposures are below those achieved at the monkey and rat no observed adverse effect levels in the 13-week toxicology studies.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Quotient Sciences must have a full medical history from each participant's general practitioner within the last 12 months, prior to enrolment in the study. Participants will be recruited from the Quotient Sciences panel or by direct advertising to the public.

Before participants are admitted to the clinic, The Over Volunteering Prevention System will be checked to ensure that each participant has not participated in a study at another site within at least 3 months of the dosing date.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

Weight

3. Body weight ≥50 kg and body mass index within the range 19.0 to 32.0 kg/m^2 (inclusive).

Sex

4. Male or female

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period until completion of the final follow up visit after the last dose of study treatment:

- Refrain from donating sperm

Plus either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 5 for at least 30 days before first dose until completion of the final follow up visit after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction from Day 1 until 3 months after the last dose. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive serum pregnancy test within 24 hours before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal (GI), endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
2. Any history of suicidal behaviour within the past 6 months or any history of attempted suicide in a participant's lifetime.
3. History of clinically significant psychiatric disorders as judged by the investigator. Depression requiring treatment in the last 2 years.
4. History of herpes zoster (shingles) reactivation.
5. History or diagnosis of obstructive sleep apnoea.
6. History of a significant respiratory disorder. Childhood asthma that has fully resolved is permitted.
7. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
8. A positive diagnostic tuberculosis (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 participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative.
9. History of GI surgery (with exception of appendectomy).
10. History of cholecystectomy or gall stones.
11. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active.
12. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
13. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35% of total).
14. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
15. Corrected QT interval (QTcF) >450 milliseconds (msec).

    Notes:

    - The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), QT interval corrected for heart rate according to 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 participant 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 participant and the lowest QTc value used to include or discontinue the participant from the trial.

- For purposes of data analysis, QTcB, QTcF, another QTc correction formula or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan.

Prior/Concomitant Therapy

16. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days prior to dosing (paracetamol/acetaminophen [up to 2 g per day], hormone replacement therapy and hormonal contraception are permitted).
17. Live or attenuated vaccine(s) within 30 days of enrolment, or plans to receive such vaccines during the study or plans to receive a vaccine within 30 days + 5 half-lives of the last dose of study medication.

Prior/Concurrent Clinical Study Experience

18. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56 day period; therefore donation or loss of greater than 400 mL of blood within the previous 3 months.
19. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
20. Current enrolment or past participation within the last 3 months before signing of consent in this or any other clinical study involving an investigational study treatment or any other type of medical research.
21. Participants who have previously been enrolled in this study. Participants in Part A of this study are not permitted to participate in Part B.

Diagnostic assessments

22. Current or history of renal disease or estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation calculation <60 mL/min/1.73m^2 at screening.
23. Presence of Hepatitis B surface antigen (HBsAg) at screening. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose. As potential for and magnitude of immunosuppression with this compound is unknown, participants with presence of hepatitis B core antibody (HBcAb) should be excluded. Participants positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
24. An elevated C-reactive protein (CRP) outside the normal reference range.
25. Confirmed positive pre-study drug/alcohol screen.
26. Positive human immunodeficiency virus (HIV) antibody test.
27. Regular use of known drugs of abuse, or history of drug or alcohol abuse in the past 5 years.

Other Exclusions

28. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer or 1 (25 mL) measure of spirits, 1.5 to 2 units is 1 glass (125 mL) of wine, depending on type.
29. Current use or history of regular use of tobacco- or nicotine-containing products within 6 months prior to screening. A carbon monoxide breath test reading of greater than 10 parts per million (ppm).
30. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
31. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
32. Total cholesterol ≥300 mg/dL (≥7.77 millimole [mmol]/Litre [L]) or triglycerides ≥250 mg/dL (≥2.82 mmol/L).
33. Participants who are study site or sponsor employees, or immediate family members of a study site or sponsor employee.

6.3. Lifestyle Considerations

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from Seville oranges and grapefruit derivatives for 24 hours before admission to each study period until after collection of the final PK sample in that period.
- Refrain from consumption of poppy seeds for 48 hours before screening, and from 48 hours before admission to each study period until after collection of the final PK sample in that period.
- For fasted dosing, no water is allowed from 1 hour before dosing until 1 hour after dosing with the exception of the 240 mL water provided with each dose. Water is allowed ad libitum at all other times.
- For fasted dosing, participants will be provided with a light snack on the evening before dosing and will be required to fast from all food and drink (except water) for a minimum of 10 hours before dosing until approximately 4 hours after dosing. Lunch will be provided approximately 4 hours after dosing, an evening meal will be provided approximately 10 hours after dosing and an evening snack will be provided approximately 14 hours after dosing.
- For dosing after a high-fat breakfast or a standard breakfast, participants will be provided with a light snack on the evening of Day -1 and will fast from all food and drink (except water) until the following morning, when they will be provided with the appropriate breakfast. The breakfast should be consumed over a maximum period of 25 minutes, with dosing occurring 30 minutes (±5 minutes, Part B Period 7

only) after the start of breakfast. Participants should be encouraged to eat their meal evenly over the 25 minutes period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 minutes after the start of breakfast. Subjects must complete 90% of the meal to be dosed. Lunch will be provided approximately 4 hours after dosing, an evening meal will be provided approximately 10 hours after dosing and an evening snack will be provided approximately 14 hours after dosing.

- For dosing before a standard meal, participants will be provided with a light snack on the evening before dosing and will be required to fast from all food and drink (except water) for a minimum of 10 hours before dosing. No water is allowed from 1 hour before dosing until 1 hour after dosing, with the exception of the 240 mL water provided with each dose. Water will be allowed ad libitum 1 hour after dosing or after administration of the standard breakfast, whichever is sooner. A standard breakfast will be provided either 30 or 60 minutes after dosing. Lunch will be provided approximately 4 hours after dosing, an evening meal will be provided approximately 10 hours after dosing and an evening snack will be provided approximately 14 hours after dosing.
- For evening dosing (Part B Period 7 only):
    - For fasted dosing, participants will be provided with a light snack on the day of dosing (Day 1) and will be required to fast from all food and drink (except water) for a minimum of 4 hours before dosing. No water is allowed from 1 hour before dosing until 1 hour after dosing, with the exception of the 240 mL water provided with each dose. Water will be allowed ad libitum 1 hour after dosing. De-caffeinated fluids will be allowed ad-libitum from 4 hours post-dose. Participants will be provided with a snack at 4 hours post-dose.
    - For dosing before a standard or high-fat meal (delayed meal), participants will be provided with a light snack on the day of dosing (Day 1) and will be required to fast from all food and drink (except water) for a minimum of 4 hours before dosing. No water is allowed from 1 hour before dosing until 1 hour after dosing, with the exception of the 240 mL water provided with each dose. Water will be allowed ad libitum 1 hour after dosing or after administration of the standard or high-fat evening meal (which will contain the same content as the breakfast), whichever is sooner. A standard or high-fat evening meal will be provided either 30 or 60 minutes after dosing. De-caffeinated fluids will be allowed ad-libitum from 4 hours post-dose. Participants will be provided with a snack at 4 hours post-dose.
    - For dosing after a high-fat or a standard evening meal (which will contain the same content as the breakfast), participants will be provided with a light snack on the day of dosing (Day 1) and will fast from all food and drink (except water), until the appropriate time when they will be provided with the appropriate meal. The meal should be consumed over a maximum period of 25 minutes, with dosing occurring 30 minutes (±5 minutes) after the start of the meal. Participants should be encouraged to eat their meal evenly over the 25 minutes period. It is acknowledged that some participants will take less

time to eat, but dosing should still occur 30 minutes after the start of the meal. Subjects must complete 90% of the meal to be dosed. De-caffeinated fluids will be allowed ad-libitum from 4 hours post-dose. Participants will be provided with a snack at 4 hours post-dose.

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before admission until after collection of the final PK sample in that period.
- Participants will abstain from alcohol for 24 hours before screening. During each dosing session, participants will abstain from alcohol from 24 hours before admission until after collection of the final PK sample in that period.
- Current smokers or users of other tobacco products will not be enrolled in this study.

6.3.2. Activity

- Participants will abstain from strenuous exercise for 72 hours before screening and then from 72 hours before admission until discharge from the study. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the investigator if the reasons for the screening failure are expected to be temporary. Rescreened participants will be assigned a new screening number and will be re-consented.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

7.1.1. Treatments Administered - Part A

Regimen	A	B	C	D	E	F
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	MR prototype Coated Tablet MR1	IR Tablet Reference	MR prototype Coated Tablet MR2	MR prototype Coated Tablet MR1, MR2 or MR3	MR prototype Coated Tablet MR1, MR2, MR3 or M4	MR prototype Coated Tablet MR1, MR2, MR3, or M4
Unit dose strength(s)/ Dosage level(s):	240 mg / 240 mg	30 mg / 240 mg	240 mg / 240 mg	240 mg / 240 mg	240 mg / 240 mg	240 mg / 240 mg
Route of Administration	Oral with 240 mL water					
Dosing instructions:	1 tablet, on the morning of Day 1 following an overnight fast	8 tablets in the morning of Day 1 following an overnight fast	1 tablet, on the morning of Day 1 following an overnight fast	1 tablet, on the morning of Day 1 following an overnight fast (if alternative formulation) or following a high-fat breakfast (if previous formulation)	1 tablet, on the morning of Day 1 following an overnight fast (if alternative formulation) or following a high-fat breakfast, standard breakfast or delayed meal (if previous formulation)	1 tablet, on the morning of Day 1 following an overnight fast (if alternative formulation) or following a high-fat breakfast, standard breakfast or delayed meal (if previous formulation)
Packaging and Labelling	100 cc HDPE white bottle	45 cc HDPE white bottle	100 cc HDPE white bottle	100 cc HDPE white bottle	100 cc HDPE white bottle	100 cc HDPE white bottle
	Each HDPE bottle will be labelled as required per country requirement.					
Manufacturer	GSK	GSK	GSK	GSK	GSK	GSK

7.1.2. Treatments Administered - Part B

Regimen	G	H	I (Optional)	J (Optional)	K (Optional)	L	M (Optional)
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	MR prototype Coated Tablet MRX	MR prototype Coated Tablet MRX	MR prototype Coated Tablet MRX or MRX1	MR prototype Coated Tablet MRX or MRX1	MR prototype Coated Tablet MRX, MRX1 or MRX2	MR prototype Coated Tablet MRX, MRX1 or MRX2	MR prototype Coated Tablet MRX, MRX1 or MRX2
Unit dose strength(s)/ Dosage level(s):	120 mg / 120 mg (may be changed following review of Part A data)	tbc / tbc	tbc / tbc	tbc / tbc	tbc / tbc	tbc / tbc	tbc / tbc
Route of Administration	Oral with 240 mL water						
Dosing instructions:	1 tablet, on the morning of Day 1 Food status: tbc	xx tablets, on the morning of Day 1 Food status: tbc	xx tablets, on the morning of Day 1 Food status: tbc	xx tablets, on the morning of Day 1 Food status: tbc	xx tablets, on the morning of Day 1 Food status: tbc	xx tablets, on the morning of Day 1 Food status: tbc	xx tablets, on the morning OR evening of Day 1 Food status: tbc

Regimen	**G**	**H**	**I (Optional)**	**J (Optional)**	**K (Optional)**	**L**	**M (Optional)**
Packaging and Labelling	100 cc HDPE white bottle labelled as required per country requirement.						
Manufacturer	Quotient	Quotient	Quotient	Quotient	Quotient	Quotient	Quotient

MRX is the formulation selected from Part A. MRX1 and MRX2 are alternative MR formulations that may be investigated from Part A. Tablets in Periods 1 and 2 will be manufactured with apertures. Tablets may be manufactured with or without apertures (i.e., drilled or non-drilled) from Period 3 onwards. Tablets without apertures will be manufactured based on a formulation which has already been dosed.

7.2. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule (see Section 5.1 and Section 5.5). The dosing regimens in Part B will be selected based on PK and safety data from participants in Part A, and the mean $AUC_{(0-24)}$ and C_{max} will not exceed a total daily dose equivalent to the systemic exposure for IR 240 mg TID (i.e., mean $AUC_{(0-24)}$ of 45.0 µg.h/mL and mean C_{max} of 4.3 µg/mL) taking into account the bioavailability of MR relative to IR (i.e., if the bioavailability of MR is 50% that of IR, the maximum daily dose of MR to be administered would be 1440 mg).

The decision on the dose of GSK2982772 to be administered in Part B will be made by the sponsor and investigator based on safety, tolerability, and PK data obtained in at least 12 participants at the prior dose level, as described in Section 5.1.3.

7.3. Method of Treatment Assignment

This is an open-label, non-randomised study. A treatment allocation list will take the place of the randomisation schedule, which will be developed by the sponsor.

At screening, a unique Subject Number will be assigned to any subject who has at least one screening procedure performed, other than informed consent. The unique Subject Number will be used to identify individual subjects during the course of the study, and will start with PPD.

A treatment allocation list will be produced by GSK Clinical Statistics prior to the start of the study, using the validated internal software, which will dictate the treatments that should be administered to each participant in each period. The master treatment allocation list will be sent to the site and retained in the ISF.

Participant numbers will be allocated on the morning of dosing of Period 1 according to the code PPD to PPD for Part A, and PPD to PPD for Part B using the lowest number available. Replacement subjects will be assigned Participant Numbers PPD to PPD for Part A and PPD to PPD for Part B.

7.4. Blinding

This is an open-label study.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.

3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the technical agreement.

- 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.

7.6. Treatment Compliance

- When participants 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 participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the source data along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Use of hormonal contraception and hormone replacement therapy is permitted provided use is stable during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required to treat AEs.

7.8. Treatment after the End of the Study

There is no treatment after the end of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

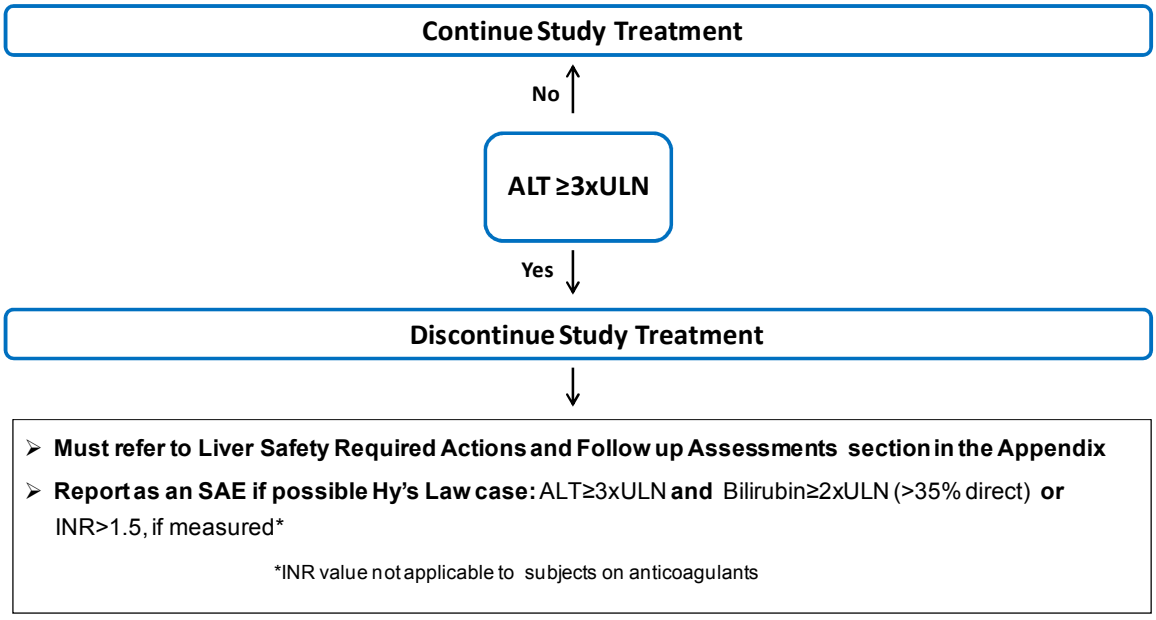
In rare instances, it may be necessary for a participant to permanently discontinue study treatment. See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm below or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes that study treatment discontinuation is in the best interest of the participant.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.1.2. QTc Stopping Criteria

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.

- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (eg, 5-10 minute) recording period.

A participant that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.

- QTc >500 msec
- Change from baseline (pre-dose Day 1) of QTc >60 msec

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Individual Safety Stopping Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator is possibly, probably or definitely related to investigational product.
- The participant becomes pregnant.
- The participant initiates treatment with any prohibited medications.
- The participant develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria or QTc stopping criteria are met.
- The participant experiences any signs of suicidal ideation or behaviour.

8.1.4. Temporary Discontinuation

If a participant is not dosed when planned in a particular period (eg, in case of unexpected personal circumstances or AEs that occur between treatment periods), they may be dosed at a later date (if a subject cannot re-attend within 28 days, they should be considered withdrawn), provided the following criteria are met:

- The AE has resolved or stabilised.
- The AE preventing dosing was not considered related to the IMP.
- The participant has not met any individual stopping criteria.
- It is considered safe to continue to dose in the opinion of the investigator.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. If a participant 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 source data.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- The Sponsor's request, for reasons such as significant protocol deviations or participant safety concern (and after discussion with the Investigator).
- If a participant is withdrawn from study treatment, this participant is also considered to be withdrawn from the study following completion of follow-up assessments.
- Study is terminated by the Sponsor.
- Refer to the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.4. Study Stopping Criteria

The study will be halted, and the risk to other participants evaluated, prior to a decision as to whether to terminate the study if any of the following criteria are met:

- A serious adverse reaction (i.e., a serious adverse event considered at least possibly related to the IMP administration) in one subject.

- Severe non-serious adverse reactions (i.e., severe non-serious adverse events considered as, at least possibly related to the IMP administration) in two subjects, independent of within or not within the same system organ class.

Relatedness will be determined by the investigator. If the study is halted, a temporary halt will be submitted to the MHRA and EC in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

8.5. Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow up measures taken for safety reasons, if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the PI or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once exposure to GSK2982772 has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe AE(s), as defined in Appendix 4, if considered to be related to the IMP.
- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in Section 3.3 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances,

termination can only take place with the agreement of the investigator and sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management or by generic screening (eg, blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL in a 70-day period.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- A participant will be allowed to leave the premises following completion of study-specific procedures at 48 hours post-dose (Part A, Treatment Periods 1, 3, 4, 5, 6 and Part B, all periods) or 24 hours post-dose (Part A, Treatment Period 2) providing that:
    - No AEs have been reported during the study visit
    - The participant responds positively when asked "How are you feeling?"

  If any of these conditions are not met, then the participant may only be allowed to leave the clinical unit with the authorisation of the investigator or appropriately qualified delegate.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the source data not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as

defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Further details can be found in Appendix 7.

9.2.5. Pregnancy

- Details of all pregnancies in female participants and, female partners of male participants will be collected after the start of study treatment and until the follow-up visit at the time points specified in the SoA (Section 2).
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of GSK2982772 greater than that intended in this study will be considered an overdose.

There is no specific antidote for overdose with GSK2982772.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 48 hours following the last dose of GSK2982772).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the source.

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 participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, heart rate and respiratory rate.
- The acceptable deviations from the nominal vital signs measurement time points are:
  - The pre-dose vital signs measurements will be taken ≤2 hours before dosing.
  - Post-dose vital signs measurements will be taken ± 15 minutes from the nominal post-dose time points.
  - Discharge vital signs measurements will be taken ± 1 hour from the nominal time point.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), must be reported as an AE.

9.4.3. Electrocardiograms

- Triplicate 12-lead ECGs will be obtained at screening and single 12-lead ECGs will be obtained as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. If a single ECG shows a QTc increase of ≥60 msec from baseline (pre-dose Day 1), two further ECGs should be performed over a brief period (eg, 5 to 10 minutes) and the assessment made on the mean QTc of the triplicate ECGs. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (eg, 5 to 10 minutes) recording period.
- The acceptable deviations from the nominal ECG measurement time points are:
  - The pre-dose ECG measurements will be taken ≤2 hours before dosing
  - Post-dose ECG measurements will be taken ± 15 minutes from the nominal post-dose time point.
  - Discharge ECG measurements will be taken ± 1 hour from the nominal time point.
- ECGs are to be measured after participant has been in a semi-supine or supine position after approximately 5 minutes rest.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), will be reported as an AE.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- Blood samples for scheduled laboratory assessments will be taken following an overnight fast.
- The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:
  - Post-dose blood samples will be taken ± 1 hour from the nominal blood sampling time except when the time point coincides with the PK blood sampling time. In this situation, the time window for the PK sample applies.
- The acceptable deviations from the nominal urine sampling time points for urinalysis are:
  - Post-dose urine samples will be taken ± 2 hour from the nominal urine sampling time.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the study database. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the source.

9.4.5. 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 disease. 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.

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

Families and caregivers of patients being treated with GSK2982772 should be alerted about the need to monitor participants 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.

9.5. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2982772 as specified in the SoA (see Section 2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM) or equivalent.
- The acceptable deviations from the nominal post-dose blood sampling times are as follows:
  - The pre-dose blood sample will be taken ≤1 hour before dosing.
  - Post-dose samples will be taken within ± 10 minutes of the nominal post-dose sampling time
- Samples will be used to evaluate the PK of GSK2982772. Samples collected for analyses of GSK2982772 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Plasma analysis will be performed under the control of Platform Technology & Science (PTS), In Vitro/In Vivo Translation (IVIVT) and Third Party Resourcing (TPR), GSK. Concentrations of GSK2982772 will be determined in plasma using the current approved bioanalytical methodology. Raw data will be archived at the Bioanalytical site as detailed in the SRM or equivalent.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

- A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study, as specified in the SoA (see Section 2). Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.
- See Appendix 8 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM or equivalent.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

No formal hypothesis will be tested. However, point estimates and corresponding 90% confidence intervals will be derived for C_{max}, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}inf)}$ and C_{24h}.

10.2. Sample Size Determination

The maximum between-subject coefficient of variation (CV_b) for the PK parameters observed in Part A of Study 205017 were used for precision estimates; CV_b (%) for $AUC_{(0\text{-}inf)}$, C_{max}, C_{18h}, C_{20h}, C_{22h}, and C_{24h} were 48.7%, 58.5%, 68.5%, 68.7%, 65.1%, and 73.2%, respectively. Therefore, the respective estimates of within subject coefficient of variation (CV_w [%]) are 30.9%, 36.7%, 42.3%, 42.5%, 40.4%, and 44.9%. Based on these estimates of variability and a sample size of 12 completers, it is estimated that the lower and upper bounds of the 90% confidence interval (CI) for the geometric mean ratio (MR/IR) of AUC and C_{max} will be within approximately 24.3% and 29.2% of the point estimate, respectively. Similarly, it is estimated that the lower and upper bounds of the 90% confidence interval for the geometric mean ratio (MR2/MR1) of C_{18h}, C_{20h}, C_{22h}, and C_{24h} will be within approximately 32.3%, 33.9%, 34.1%, and 36.2% of the point estimate, respectively.

Since it is expected that the MR1 tablet formulation vs IR is to reduce C_{max} by 80% and AUC by 40%, a sample size of 12 ensures that the 90% CI is within the region 0.459-0.796 for AUC and 0.132-0.310 for C_{max} if the observed geometric ratio is 0.57-0.64 for AUC and 0.17-0.24 for C_{max}. Since it is expected that the MR2 tablet formulation will increase C_{18h}, C_{20h}, C_{22h}, and C_{24h} by 28%, 43%, 44%, and 27%, respectively vs MR1, a sample size of 12 ensures that the 90% CI is within the region 0.945-1.746 for C_{18h}, 1.046-1.968 for C_{20h}, 1.051-1.985 for C_{22h}, and 0.910-1.784 for C_{24h} if the observed geometric mean ratio is 1.25-1.32 for C_{18h}, 1.40-1.47 for C_{20h}, 1.41-1.48 for C_{22h}, and 1.24-1.31 for C_{24h}.

Sample Size Sensitivity

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability observed in Part A of Study 205017, the precision of these estimates calculated as half width of a 90% confidence interval for the mean ratio (MR/IR or MR2/MR1) and expressed as distance from mean to limits for 10, 12, 14 and 16 participants has been calculated (Table 3).

Table 3 Precision Estimate of Mean Ratio

Parameter	CVw (%)	Precision of Mean Ratio (%)			
		N=10	N=12	N=14	N=16
AUC	30.9	27.5	24.3	22.0	20.3
C_{max}	36.7	33.1	29.2	26.4	24.3
C_{18h}	42.3	36.7	32.3	29.2	26.8
C_{20h}	42.5	38.6	33.9	30.6	28.1
C_{22h}	40.4	38.8	34.1	30.8	28.3
C_{24h}	44.9	41.1	36.2	32.6	29.9

For example, based upon the estimate of variability (CV_w%) of 30.9 and a sample size of 16, it is estimated that the lower and upper bounds of the 90% confidence interval for the geometric mean ratio of the PK parameter (eg, AUC, C_{max}) will be within approximately 20.3% of the point estimate.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Subjects	All participants who receive at least 1 dose of study treatment and will be the population for reporting of safety and study population data. Participants will be analyzed according to the treatment they actually received.
PK	Participants in the 'All Subjects Population' for whom a PK sample was obtained and analysed and will be the population for reporting of PK data.

10.4. Statistical Analyses

10.4.1. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population.

For both parts of the study, plasma GSK2982772 concentration-time data will be analysed by non-compartmental methods.

The plasma concentration-time data for each of the regimens, the following PK parameters will be determined, as data permit:

- maximum observed plasma concentration (C_{max}).
- time to C_{max} (T_{max}).
- the elapsed time from dosing at which GSK2982772 was first quantifiable in a concentration vs time profile (T_{lag}).
- observed concentration at 24 hours post-dose (C_{24h}).
- observed concentration at 8 and 12 hours post-dose (C_{8h} and C_{12h}) for IR only.
- area under the plasma concentration vs time curve ($AUC_{(0-t)}$, $AUC_{(0-24)}$ and $AUC_{(0-inf)}$).
- the percentage of AUC extrapolated beyond the last measured time point (AUC%extrap).
- terminal half-life ($t_{1/2}$).
- relative bioavailability ($Frel_{formulation}$) of test formulations (under fed or fasted conditions) vs reference formulation based on $AUC_{(0-24)}$ and $AUC_{(0-inf)}$ (or $AUC_{(0-t)}$ if $AUC_{(0-inf)}$ can't be derived) and C_{max}.
- relative bioavailability ($Frel_{FE}$) of fed (high-fat breakfast or high-fat evening meal, standard breakfast or standard evening meal or delayed meal (30 or 60 minutes) vs fasted based on AUC and C_{max}.
- relative bioavailability (Frel(time effect) of evening dosing vs morning dosing based on AUC and C_{max})
- relative bioavailability ($Frel_{MRFormulation}$) of MR prototype coated tablet formulations relative to each other, as appropriate, based on AUC and C_{max} (optional Part B only)
- C_{max}/Dose and AUC/Dose (optional Part B only)

Descriptive statistics (n, arithmetic mean, standard deviation [SD], 95% CI, minimum, median and maximum) will be calculated by treatment for all PK concentrations over time and for the derived PK parameters. In addition, for $\log_e$-transformed PK parameter variables geometric mean, 95% CI and $\%CV_b$ ($100 * \sqrt{(\exp(SD2) - 1)}$) will be provided, where the SD is the standard deviation of log-transformed data.

Endpoint	Statistical Analysis Methods
Primary	The primary PK endpoints to compare MR formulations with IR formulations will be summarised descriptively. Ratios of $AUC_{(0-inf)}$, $AUC_{(0-24)}$, ($AUC_{(0-t)}$, if $AUC_{(0-inf)}$ cannot be derived), C_{max}, C_{24h} for MR formulation to IR formulation will be computed with 90% CI.
Primary	The primary endpoints for food effect will be summarised descriptively. In addition, log-transformed $AUC_{(0-inf)}$ ($AUC_{(0-t)}$, if $AUC_{(0-inf)}$ cannot be derived), C_{24h}, and C_{max} will be analysed using a mixed effects model with regimen as a fixed effect and subject within sequence as a random effect. Point estimates and corresponding 90% CI will

Endpoint	Statistical Analysis Methods
	be computed for the differences in GSK2982772 MR formulation taken in the fed state (test) vs in the fasted state (reference) using the residual error from the model (MSE). The point and interval estimates on the log-scale will then be exponentially back transformed to give estimates of the ratios of geometric means and 90% CI. Within-subject coefficients of variation for $AUC_{(0\text{-}inf)}$ and C_{max} will be calculated based on the log_e-Normal distribution: CV_w (%) = sqrt[exp(mse) - 1] x 100, where MSE is the residual error from the model. Statistical analysis of the PK endpoint T_{max} of GSK2982772 MR formulation administered under both fed and fasted conditions will be separately analysed non-parametrically [Hauschke, 1990]. The point estimates for the medians for each treatment, the median difference and 90% CI for the median difference will be calculated for the contrast (test-reference).
Secondary	The secondary PK endpoints for the selected MR formulations at different tablet strengths and multiple dose units will be summarised descriptively. For Part B, plots of dose vs dose normalised $AUC_{(0\text{-}24)}$, C_{24h} and C_{max} will be generated to determine if there are any dose dependent changes in the absorption of GSK2982772 following administration of different tablet strengths and multiple dose units of the selected MR formulation(s). For Part B, dose proportionality will be assessed by visual inspection of dose normalised $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}inf)}$ [or if not available $AUC_{(0\text{-}t)}$] and C_{max} values versus dose. Analysis of these log_e-transformed parameters may be carried out, using the power model. For Part B Period 7, the relative bioavailability of time effect (Frel(time effect)) will be assessed by comparing $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max}, between evening dosing (test) versus morning dosing in the same prandial state (reference).

The Reporting and Analysis Plan will describe the planned PK analyses in greater detail.

10.4.2. Safety Analyses

All safety analyses will be performed on the All Subjects Population.

Endpoint	Statistical Analysis Methods
Secondary	The safety endpoints will be summarised descriptively.

The Reporting and Analysis Plan will describe the planned safety analyses in greater detail.

10.4.3. Interim Analyses

No formal statistical analyses are planned. However, after Periods 1 to 3, 4 and 5 of Part A are complete, the PK data will be analysed which will guide Periods 4, 5 and 6. Periods 4, 5 and 6 will be flexible and the dosing regimen will be dependent on the outcome (safety and PK) of preceding periods. There will be the option to optimise the MR release duration and/or to evaluate the impact of a high-fat meal on the selected MR formulation(s). If an optimal formulation is identified in Part A, Part B will proceed. If none of the MR prototype coated tablet formulations are suitable, then Part B of the study may not be conducted or Part B may be used to continue to optimise the MR prototype coated tablet formulations. This will be based upon identifying a formulation that has an appropriate exposure profile that does not show a significant food effect.

In Part B, there will be an interim review following completion of each of Periods 1 to 5 to determine the dose level, formulation and prandial status, as appropriate, to be used in subsequent periods. There will also be an interim review following completion of Period 6 to determine if optional Period 7 is required and the dose level, dosing time (morning or evening), formulation and prandial status for that period.

See Section 5.1.3 for full details on the criteria for interim decisions.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.4.4. Stopping Criteria

After data is available and analysed for Period 1, 2 and 3 in Part A, a decision to stop the study could be triggered if:

- The PK profile of IR and MR are similar, based on visual judgement of concentration-time curves. Consideration of PK parameters, $AUC_{(0\text{-}inf)}$ and C_{max} will assist with this judgement but no formal quantitative no-go will be defined due to the exploratory and flexible nature of the study.

11. REFERENCES

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 & Differ*, 2013;20:1381-92.

GlaxoSmithKline Document Number 2014N204126_03. GSK2982772 Investigator Brochure. Effective Date 25-JAN-2018

Hauschke D1, Steinijans VW, Diletti E. A distribution-free procedure for the statistical analysis of bioequivalence studies. *Int J Clin Pharmacol Ther Toxicol*, 1990;28(2):72-8.

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.

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.

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

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ALS	Amyotrophic lateral sclerosis
AST	Aspartate Aminotransferase
AUC	Area under the concentration vs time curve
$AUC_{(0\text{-}inf)}$	Area under the curve from time zero to infinity
$AUC_{(0\text{-}24)}$	Area under the curve from time zero to 24 hours
$AUC_{(0\text{-}t)}$	Area under the curve from time zero to the last measurable concentration
BID	Twice daily
BUN	Blood Urea Nitrogen
C_{24h}	Concentration at 24 h post-dose
CA	Competent Authority
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
Cmin	Minimum observed concentration
CPMS	Clinical Pharmacokinetics Modelling and Simulation
CPK	Creatine phosphokinase
CNS	Central nervous system
CO2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
CSR	Clinical Study Report
CV	Cardiovascular
CV_b	Between subject coefficient of variation
CV_w	Within subject coefficient of variation
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
FTIH	First time in human
FreI	Relative bioavailability
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GD	Gestation day
GI	Gastrointestinal
GLP	Good Laboratory Practice
GNA	Grounds for Non-Acceptance

GSK	Glaxosmithkline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human Chorioninc Gonadotropin
HIV	Human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hypromellose
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committees
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
INR	International normalized ratio
IR	Immediate release
IRB	Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVIVT	In Vitro/In Vivo Translation
L	Litre
Kg	Kilograms
LD	lactation day
LDH	Lactate dehydrogenase
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDMA	3,4-methylenedioxy-methamphetamine
Mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minute
mL	Millilitres
Mmol	Millimole
MR	Modified release
MSDS	Material Safety Data Sheet
MS	Multiple sclerosis
Msec	Milliseconds
NOAEL	No observed adverse effect level
NSA	Non-substantial amendments
Pgp	P-glycoprotein
PGx	Pharmacogenomics
PI	Principal investigator
PIS	Participant Information Sheet
PK	Pharmacokinetic(s)
PND	Post-natal day
Ppm	Parts per million
PsO	Plaque psoriasis

PTS	Platform Technology & Science
QD	Once daily
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RA	Rheumatoid arthritis
RBC	Red blood cells
RIP1	Receptor-interacting protein-1
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SIB	Suicidal ideation and behaviour
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of activities
SRM	Study Reference Manual
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TID	Three times daily
TLR	Toll like receptor
T_{max}	Time to C_{max}
T1/2	Terminal half-life
TNF	Tumour necrosis factor
TPR	Third Party Resourcing
ULN	Upper limit of normal
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
LAMICTAL XR

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by The Doctors Laboratory, with the exception of routine urinalysis, urine pregnancy test, urine drug screen, alcohol and carbon monoxide breath tests. These tests will be performed on-site.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- 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.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count Red Blood Cell (RBC) Count Haemoglobin Haematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) %Reticulocytes		White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin (direct only if total is elevated)
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Chloride	Cholesterol (Total)	Triglycerides	
Routine Urinalysis	• Specific gravity			

Laboratory Assessments	Parameters
	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick • Microscopic examination (if blood, protein or leukocytes are abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) at screening only • urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • alcohol breath test • carbon monoxide breath test • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Serum hCG pregnancy test (as needed for women of childbearing potential) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb] and hepatitis C virus antibody) at screening only • Tuberculosis test (QuantiFERON) at screening only • C-reactive protein (CRP) at screening only The results of each test must be entered into the source.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

12.3. Appendix 3: Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Prior to the initiation of the study, the Clinical Trial Authorisation application must be approved by the MHRA. A copy of this approval and any correspondence with the MHRA will be available at the clinical and sponsor sites. A copy of the MHRA approval will be provided to the EC.
- Any substantial amendments to the protocol will require MHRA and IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants (urgent safety measure).
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Protocol Amendments and Deviations

Amendments

After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.

If the participant information sheet (PIS) and ICF are updated as a result of an amendment, the new versions will be used to re-consent currently enrolled participants and must be provided to additional participants prior to their entry into the study.

Protocol Deviations

The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances should be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded in the source data as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria stated in Section 8 have been met.

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- Participants will be provided with a written explanation of the study at least one day before the screening visit.
- The investigator or his/her representative will explain the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation to the participant and answer all questions regarding the study. Participants will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The source data must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Following completion of the study, a clinical study report will be prepared.
- 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 and will be made available to the EC/MHRA within 1 year of the declaration of the end of trial.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic source unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the source.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the study database.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing data verification to confirm that data entered into the study database by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data captured into the study database that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- A study-specific source documentation list will be finalised by the sponsor before the start of the clinical phase of the study. The document will identify what data should be considered source data for this study.

Declaration of the End of the Study

The definition of the end of the study is defined as the point at which the sponsor determines that any remaining optional groups are not required to meet the objectives of the trial ie signed dose decision document. If all optional groups are used, completion of the last follow-up visit will be considered the end of the study. Any changes to this definition will be notified as a substantial amendment.

The EC and MHRA should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting to GSK

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• 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 participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include 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.

Definition of an Adverse Drug Reaction (ADR)

An ADR is defined as any untoward medical occurrence that, at any dose:
• where a causal relationship with the IMP is at least a reasonable possibility (possibly related or related)

Definition of SUSAR

A SUSAR is defined as any untoward medical occurrence that, at any dose:
• Is believed to be related to an IMP and is both unexpected (ie the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the MHRA, European Medicines Agency (EMA), EC (see Appendix 7)

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the source (ie the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study treatment and the event). • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE source. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities; intervention may be needed.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory

reporting requirements.
Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed source data. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the study database (eg, check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the study database. • After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the Communication Plan.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Communication Plan.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (ie ≥ 40 IU/L) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Table 5 Highly Effective Contraceptive Methods

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • Oral
  • Injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing will be performed at admission to each study period and discharge from each study period
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

  Urine pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the SureScreen Diagnostics test in accordance with instructions provided in its package insert at each admission. Serum pregnancy testing, with a sensitivity of 5.8 mIU/mL will be performed and assayed in the certified local laboratory (The Doctors Laboratory)

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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

Any female participant who becomes pregnant while participating will be withdrawn from the study

12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event source, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin <2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 2 days of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including paracetamol/acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:</td></tr>
</table>

liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilise or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy source 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. 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
4. 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 PK blood sample draw on the source. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

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

12.7. Appendix 7: Safety Reporting to Ethics Committee and Regulatory Authorities

Events Requiring Expedited Reporting

SUSARs are subject to expedited reporting to the MHRA, EMA and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the participant has completed the clinical study where the sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the participants, such as:
  - an SAE which could be associated with the study procedures and which could modify the conduct of the study
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another country by the same sponsor

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

Expedited Reporting of Events

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

<u>Fatal or life-threatening SUSARs</u>

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

Urgent Safety Measures

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of participants enrolled in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study participants.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the EC.

Reporting of Urgent Safety Issues

Quotient Sciences is required to inform the appropriate competent authorities and the EC within 3 calendar days of the urgent safety issue.

Serious Breaches

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the participants of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

12.8. Appendix 8: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK2982772 or immuno-inflammatory and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2982772 (or study treatments of this drug class) and immuno-inflammatory diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed for UDP-glucuronosyltransferase 1-9 family, polypeptide A cluster enzyme that is encoded by the UGT1A9 gene complex. Additonal analyses may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2982772 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2982772 (or study treatments of this class) continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

12.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 28-AUG-2018

Overall Rationale for the Amendment:

This amendment addresses the Grounds for Non-Acceptance (GNA) received by MHRA noting that an Investigator should only have the responsibility of determining causality of a SAE or severe clinically significant AE without sponsor consultation.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.3	Removal of GSK MM consultation for determining causality of a SAE or severe clinically significant AE.	The determination of causality for individual subject withdrawal should be at the responsibility of an Investigator only.

Amendment 2 26 FEB 2019

Overall Rationale for the Amendment

This amendment includes a new investigational medicinal product (IMP), requested by the sponsor, in order to compare the type of coating for GSK2982772 Modified Release (MR) prototype coated tablets. This substantial amendment will also incorporate protocol non-substantial amendments (NSA) 03 to 06, which were implemented after Amendment 1 approval date 28 AUG 2018.

Section # and Name	Description of Change	Brief Rationale
Synopsis – Rationale and Overall Study Design, Section 3.2 – Study Rationale, Section 5.1 – Overall Study Design, Section 5.1.2 – Part B, Figure 2 – Part B Study Design – Tablet Strength, Section 5.4 – Scientific Rationale for Study Design, Section 7.1.2 – Treatments Administered – Part B	The clinical protocol currently only allows variance of the polymer content of the tablets core. Tablets are currently manufactured with an aperture on either side of the tablet (i.e., drilled). A new IMP will be manufactured without apertures (i.e., full coat/non-drilled).	The sponsor would like to compare the current modified release tablet, which has an aperture drilled into the coating on each side of the tablet, with a fully coated tablet. The composition of the coat will not change between formulations. An additional IMP will be manufactured to allow comparison of the tablet coating - without apertures (i.e., full coat/non-drilled) or with apertures (i.e., drilled).
Section 7.1 – Treatments Administered	Updates made based on protocol Non-Substantial Amendment 03. The MR prototype tablets will be provided in a 100 cc HPDE white bottle (corrected from 85 cc)	The packaging details for the MR prototype coated tablets are incorrect. The MR prototype coated tablets will be supplied in 100 cc HDPE bottles instead of 85 cc HDPE bottles.
Synopsis – Overall Design, Treatment Groups and Duration, Table 1- Schedule of Activities for Parts A and B, Table 2 – Pharmacokinetic Blood Sample Collection Times – Parts A and B, Section 5.1.1 – Part A, Section 5.1.3 – Criteria for Interim Decisions, Section 7.1.1 – Treatments Administered –	Updates made based on protocol Non-Substantial Amendment 04. Update to the period in which the immediate release (IR) tablet is dosed. The IR tablet will be dosed in Period 2 (Regimen B) and the MR prototype coated tablet MR2 will be dosed in Period 3 (Regimen C).	The Sponsor requested that the immediate release reference tablet is to be dosed in Period 2 instead of Period 3. There have been some issues with some of the supplied modified release tablet batches and the Sponsor required time to investigate the quality of the product and assess if a re-manufacture was required before dosing in the clinic.

Section # and Name	Description of Change	Brief Rationale
Part A and Section 9 – Study Assessments and Procedures		
Synopsis –Overall Rationale and Study Design, Section 5.1.2 – Part B, Figure 2 – Part B Study Design – Tablet Strength, Section 5.4 – Scientific Rationale for Study Design and Section 7.1.2 – Treatments Administered – Part B	Updates made based on protocol Non-Substantial Amendment 05. Updated to allow multiple dosing units to be administered in Part B, Periods 2 to 6.	Following review of clinical data from Part A of this study and data generated as part of other studies used for dose prediction, the highest dose in Part B would require dosing multiple units rather than only one tablet of high strength. The sponsor would like to have the option to dose at a higher strength based on emerging data.
Section 3.3 – Benefit/Risk Assessment	Updates made based on emerging safety results from two ongoing GSK2982772 studies, Study 205184 and Study 205017.	The protocol has been updated to incorporate available data describing number of subjects dosed and safety from two ongoing GSK2982772 studies.
Figure 2 – Part B Study Design – Tablet Strength and Section 7.1.2 – Treatments Administered – Part B	Updates made based on protocol Non-Substantial Amendment 06. Updates to allow an alternative formulation which has already been dosed previously to be dosed in Part B Periods 3 to 5.	The protocol currently only allows for an alternative composition of tablet to be dosed in Part B Periods 3 to 5. Following review of clinical data from Part B Periods 1 and 2, the sponsor would like to have the option to dose a formulation which has already been dosed previously at an alternative dose level in Part B Periods 3 to 5.
Minor formatting corrections made throughout.		