TITLE PAGE

Protocol Title: A three part, non-randomised, open label study designed to assess the pharmacokinetics of GSK2982772 following administration of minitab modified release formulations in a capsule relative to an immediate release reference tablet formulation (Part A), the pharmacokinetics of escalating, repeat doses of a selected minitab modified release prototype (Part B), and the pharmacokinetics of GSK2982772 following administration of modified release tablet formulations in the fed and fasted state (Part C) in healthy participants

Protocol Number: 205017/02

Short Title: A study to compare the pharmacokinetics of GSK2982772 following administration of different minitab modified release formulations in capsule relative to an immediate release tablet formulation, to investigate the pharmacokinetics of a selected minitab modified release formulation in capsule following repeat doses for 3 days, and to compare the pharmacokinetics of GSK2982772 following administration of modified release tablet formulations in the fed and fasted state relative to an immediate release tablet formulation.

Compound Number: GSK2982772

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): EudraCT Number 2017-000652-25

Approval Date: 14-JUN-2018

SPONSOR SIGNATORY:

PPD

JUNE 14th 2018

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Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	*14-Jun-2018*
Amendment 01	*18-Sep-2017*
Original Protocol	*07-Jul-2017*

Amendment 02 14-Jun-2018

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Sections throughout protocol	Addition of Part C	Part C has been included to investigate a MR tablet formulation as the minitab capsule formulations were susceptible to a food effect
Sections throughout protocol and title	Term “Subject” has been replaced by “Participant”.	Terminology updated within GSK.
In addition, the protocol has been updated with NSA02, dated 11 Oct 2017 and NSA05, dated 23 Feb 2018		

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1. SYNOPSIS

Protocol Title: A three part, non-randomised, open label study designed to assess the pharmacokinetics of GSK2982772 following administration of minitab modified release formulations in a capsule relative to an immediate release reference tablet formulation (Part A), the pharmacokinetics of escalating, repeat doses of a selected minitab modified release prototype (Part B), and the pharmacokinetics of GSK2982772 following administration of modified release tablet formulations in the fed and fasted state (Part C) in healthy participants.

Short Title: A study to compare the pharmacokinetics of GSK2982772 following administration of different minitab modified release formulations in capsule relative to an immediate release tablet formulation, to investigate the pharmacokinetics of a selected minitab modified release formulation in capsule following repeat doses for 3 days, and to compare the pharmacokinetics of GSK2982772 following administration of modified release tablet formulations in the fed and fasted state relative to an immediate release tablet formulation.

Rationale: The purpose of this study is to evaluate a modified release (MR) formulation of GSK2982772 using a minitab approach filled into a capsule in order to develop a more convenient once daily (QD) dosing formulation. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. Initially, the pharmacokinetic (PK) profiles of slow (approximately 24 hours) and fast (approximately 10 hours) release rates of MR minitab will be compared to the PK profile of the immediate release (IR) tablet. In subsequent arms of the study, the release rate may be adapted to achieve the target PK profile. The effect of a high fat meal on the absorption of GSK2982772 when co-administered with the selected minitab MR formulation will be evaluated to ensure that dose dumping does not occur. In addition, the PK profile of repeat doses at 3 dose levels will be evaluated to ensure that the MR formulation can achieve a sufficient GSK2982772 systemic exposure range to support the Phase IIb dose ranging (DR) studies. Part C of the study has been included to evaluate the PK profile of single doses of MR tablet formulations of GSK2982772. The formulations will be evaluated at up to 4 dose levels and compared to the PK profile of the IR tablet. The 240 mg MR tablet will have a fixed composition; however, for the 360 mg and 480 mg tablets polymer compositions may be adjusted as part of a 'design space concept' to try to optimize the in vivo performance of 360 mg and /or 480 mg tablets based on the PK of the 240 mg MR tablet formulation, if required. This adjustment will be done ahead of dosing to select a formulation at each dose unit to achieve an adjusted in vivo profile based on the PK of the 240 mg MR tablet formulation. The effect of a standard meal on the PK profile of GSK2982772 will also be investigated. The effect of a high fat meal, a delayed standard meal, twice daily dosing (BID) or dosing of multiple dose units may also be investigated, if required.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each test minitab MR formulation in a capsule (120 mg) compared to the IR formulation (120 mg**)**	• 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 ($AUC_{(0\text{-}24)}$), area under the curve from time zero to 12 hours ($AUC_{(0\text{-}12)}$), maximum observed concentration (C_{max}), Concentration at 12 hours post-dose (C_{12h}), Concentration at 24 hours post-dose (C_{24h}) and ratio of C_{max} : C_{12h} and C_{max} : $C_{24h,}$ relative bioavailability ($FreI_{formulation}$) based on AUC and C_{max}
• To evaluate the single dose PK profile of GSK2982772 from a MR tablet (240 mg) compared to the IR formulation (240 mg**)**	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$, C_{max}, C_{12h}, C_{24h} and ratio of C_{max} : C_{12h} and C_{max} : $C_{24h,}$ $FreI_{formulation}$ based on AUC and C_{max}
Secondary	
• To assess the impact of high fat meal on the PK of GSK2982772 following single dose administration of the selected minitab MR formulation in a capsule (120 mg)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t),}$ C_{max} and time to C_{max} (T_{max}), $FreI_{FE}$ based on AUC and C_{max}
• To determine if there are any dose dependant changes in the absorption of GSK2982772 following repeat dose administration of the selected minitab MR formulation in a capsule at target daily doses of 30, 60 and 240 mg	• GSK2982772 $AUC_{(0\text{-}24)}$, C_{max} and T_{max} if once daily (QD) dosing, on Day 1 and Day 3 • GSK2982772 $AUC_{(0\text{-}12)}$, $AUC_{(12\text{-}24),}$, C_{max} and T_{max} after morning dose, C_{max} and T_{max} after evening dose if BID dosing, on Day 1 and Day 3

Objective	Endpoint
• To assess the impact of food on the PK of GSK2982772 following single dose administration of the MR tablet (dose corrected, as appropriate)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$ or $AUC_{(0\text{-}24)}$, C_{max} and time to C_{max} (T_{max}), $FreI_{FE}$ based on AUC and C_{max} (dose corrected, as appropriate)
• To determine if there are any dose dependent changes in the absorption of GSK2982772 following single dose administration or BID dose administration of the MR tablet	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, C_{max}, C_{24h} and ratio of C_{max} : C_{24h}, and T_{max} • GSK2982772 $AUC_{(0\text{-}12)}$, C_{12h}, and ratio of C_{max} : C_{12} if BID dosing
• To assess the safety and tolerability of single doses of GSK2982772 IR formulation and single and repeat doses of the MR formulation in a capsule, and single doses or BID dose of the MR tablet	• 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
Exploratory	
• To assess the impact of a standard meal on the PK of GSK2982772 following administration of the selected minitab MR formulation in a capsule	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $FreI_{FE}$ based on AUC and C_{max} (dose corrected as appropriate)

Overall Design:

This is an open label, single centre, three part, single and repeat dose study in healthy male and female participants to assess MR minitab formulations of GSK2982772 in a capsule. Assuming a suitable MR minitab formulation in a capsule is identified, the impact of food (high-fat meal) on the rate and extent of absorption will be evaluated as well as an assessment of the relationship between dose and systemic exposure to GSK2982772 following repeat dosing for 3 days. MR tablet formulations of GSK2982772 will also be investigated, along with the impact of food on the rate and extent of absorption.

Part A of the study is a non-randomised 6 period, sequential, 6-way fixed sequence design in which up to 4 MR minitab formulations in a capsule may be evaluated following single dose administration in the fasted state (120 mg). Periods 1, 2 and 3 will evaluate a slow MR release duration (nominally 24 hours), a fast MR release duration (nominally 10 hours), and IR tablet, 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/or to evaluate the impact of food (high-fat meal) on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 2.

Part B of the study will be an open-label, repeat dose study in which the selected MR minitab formulation in a capsule will be evaluated following 3 days repeat dosing of GSK2982772 at target daily doses of 30, 60 and 240 mg. In Part B, administration of the MR minitab formulation in a capsule will either be in the fasted state or with a standard meal (non-high fat), depending on the results of the food effect assessment in Part A. The prandial state for each dosing period may be selected as fasted or fed (standard meal) but within each dosing period, all doses will be administered in the same prandial state. The frequency of dosing in Part B will either be QD or BID depending on the PK profile in Part A. Whether dosing is QD or BID, the total daily doses will remain the same.

Part C of the study is a non-randomised 6 period, sequential, fixed sequence crossover design in which MR tablet formulations will be evaluated. Periods 1 and 2 will evaluate single dose administration of a 240 mg MR tablet and the 240 mg IR tablet (reference), respectively. Periods 3, 4, 5 and 6 will be flexible and the dosing regimen will be dependent on the outcome of Periods 1 and 2. In Periods 3 to 6, there will be the option to evaluate higher doses, the impact of a high-fat meal and/or standard meal after dosing or BID dosing.

Number of Participants:

Sixteen participants will be enrolled into Part A of the study to allow for the completion of at least 12 evaluable participants. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen). 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.

Ten participants will be enrolled into Part B of the study to allow for the completion of at least 6 evaluable participants. An evaluable participant will have received all 3 doses and completed the planned safety and PK assessments up to 24 hours after the last dose.

In Part C, 16 participants will be enrolled such that at least 12 evaluable participants complete the study. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 2; IR regimen). An evaluable participant must also have received the relevant test and reference formulations for the comparisons of interest e.g. the MR tablet and the IR reference at 240 mg.

Treatment Groups and Duration:

In Part A, each participant will be enrolled in the study for approximately 8 to 13 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. 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 3 days and 2 nights followed by a minimum washout of 7 days between doses.

A follow-up visit will occur at least 7 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 9 weeks. Participation will include a screening evaluation within 28 days of study treatment administration and 3 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 5 day, 4-night inpatient period with a minimum of 7 days washout between the last morning dose of one period and the first dose of the next period. A follow-up visit will occur at least 7 days after the last study treatment.

In Part C, each participant will be enrolled in the study for approximately 8 to 13 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. 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 3 days and 2 nights followed by a minimum washout of 7 days between doses. A follow-up visit will occur at least 7 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period (if BID dosing is selected for Period 6, participants will receive 2 doses of study treatment in this inpatient period).

2. SCHEDULE OF ACTIVITIES (SOA)

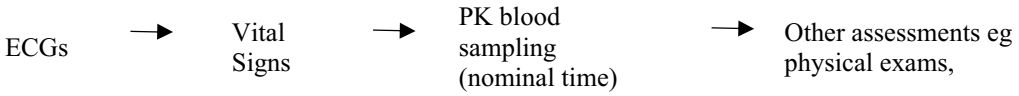
The schedules of activities for Parts A and C are presented in Table 1, and are presented in Table 3 for Part B. The time points for the PK blood sample collection in Parts A and Care presented in Table 2, and are presented in Table 4 for Part B, respectively.

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 pharmacokinetic 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:



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 C

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes[a]
		–1	1	2		
Informed consent	X					
Inclusion and exclusion criteria[1]	X					1. Recheck clinical status before 1st dose of study medication.
Demography	X					
Demonstrate ability to swallow size 0-00 capsules	X					
Full physical examination including height and weight	X					
Brief physical examination		X		X[2]	X	2. Discharge (32 h post-dose for Treatment Period 1, 2, 4, 5 and 6 in Part A and Treatment Period 1, 3, 4, 5 and 6 in Part C 24 h post-dose for Treatment Period 3 in Part A and Treatment Period 2 Part C)
Medical history (includes substance usage)[3]	X					3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X					

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes[a]
		–1	1	2		
Follicle Stimulating Hormone (FSH) (as needed in women of non-childbearing potential only)	X					
Serum pregnancy test (WOCBP only)	X				X	
Urine pregnancy test (WOCBP only)		X				
Human Immunodefeciency Virus (HIV), Hepatitis B and C screening[4]	X					4. 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	X[5]	X[5]	X	5. Pre-dose (Treatment Period 1 only) and 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 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes[a]
		–1	1	2		
12-lead ECG	X[6]	X	X[7]	X[8]	X	6. In triplicate 7. Pre-dose and 2 and 12 h post-dose 8. 24 h post-dose Allowable windows in Section 9.4.3
Vital signs	X	X	X[9]	X[10]	X	9. Pre-dose and 2 and 12 h post-dose 10. 24 h post-dose Allowable windows in Section 9.4.2
Study treatment			X			
AE review		←==========		==========→	X	
Serious AE (SAE) review	X	←==========		==========→	X	
Concomitant medication review		←==========		==========→	X	
PK blood sample collection			X[11]	X[11]		11. Time points in Table 2

[a] The timing of assessments may be amended in Part C if BID dosing is selected for any of the regimens.

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

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

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

[a] PK sampling schedule may be amended in Part C if BID dosing is selected for any of the regimens. If BID dosing is employed the number of PK samples may be reduced i.e. some of the samples between 14 and 24 h may not be required. In addition, the 12 h sample will be taken prior to administering the second daily dose.

Table 3 Schedule of Activities for Part B

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
Informed consent	X							
Inclusion and exclusion criteria[1]	X							1. Recheck clinical status before 1st dose of study medication.
Demography	X							
Demonstrate ability to swallow size 0-00 capsules	X							
Full physical examination including height and weight	X							
Brief physical examination		X				X[2]	X	2. Discharge (24 h after the last dose)
Medical history (includes substance usage)[3]	X							3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X							
FSH (as needed in women of non-childbearing potential only)	X							
Serum pregnancy test (WOCBP only)	X						X	
Urine pregnancy test (WOCBP only)		X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
HIV, Hepatitis B and C screening[4]	X							4. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Tuberculosis 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	X[5]			X[6]	X	5. Pre-dose 6. 24 h after the last dose Allowable windows in Section 9.4.4
Glomerular filtration rate	X							
CRP	X							
ANA	X					X[7]		7. 24 h after the last dose

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
12-lead ECG	X[8]	X	X[9]	X[10]	X[9]	X[11]	X	8. In triplicate 9. Pre-dose and 2 and 12 h post-dose 10. Pre-dose 11. 24 h after the last dose Allowable windows in Section 9.4.3 Time points may be subject to change depending on results from Part A
Vital signs	X	X	X[12]	X[13]	X[12]	X[14]	X	12. Pre-dose and 2 and 12 h post-dose 13. Pre-dose 14. 24 h after the last dose Allowable windows in Section 9.4.2 Time points may be subject to change depending on results from Part A
Columbia Suicide Risk questionnaire	X		X[15]			X[16]		15. Pre-dose 16. 24 h after last dose of each period
Study treatment			X	X	X			
AE review		←==========				==========→	X	
SAE review	X	←==========				==========→	X	
Concomitant medication review		←==========				==========→	X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
PK blood sample collection			X[17]	X[17]	X[17]	X[17]		17. Time points in Table 4

Table 4 Pharmacokinetic Blood Sample Collection Times – Part B

	Periods 1, 2 and 3													
	Days 1 and 3													
Time (h)	**Pre-dose**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Dosing[a]		X												
PK sampling[b]	X		X	X	X	X	X	X	X	X	X	X	X	X[c]

[a] Participants will be dosed on Days 1, 2 and 3; however, no PK samples will be taken post-dose on Day 2

[b] PK sampling schedule may be amended based upon the PK data from Part A and/or if BID dosing is selected for Part B. If BID dosing is employed the number of PK samples may be reduced i.e. some of the samples between 14 and 24 h may not be required. In addition, the 12 h sample will be taken prior to administering the second daily dose.

[c] Day 1 24 h post-dose sample should be taken prior to dosing on Day 2.

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. Study Rationale

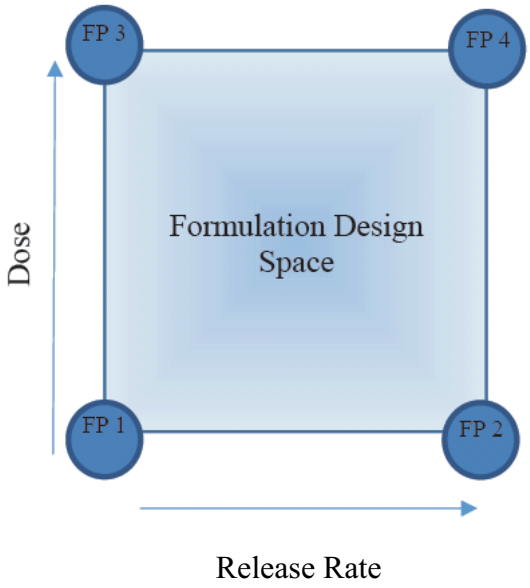
Pharmacokinetic data from the first time in human (FTIH) study for GSK2982772 (200975) [GlaxoSmithKline Document Number 2014N204126_03] showed that the half-life of GSK2982772 was short (~2 to 3 hours). As a result, BID and three times daily (TID) dosing regimens are being evaluated in three ongoing proof of mechanism studies. A QD formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. This current study is being conducted to evaluate the feasibility of developing an MR formulation using a minitab approach filled into a capsule. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. In addition, the number of minitabs included in the capsule can be varied to adjust the dose.

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.

There will be the option to test a range of formulations based on a 2-dimensional design space describing the dose level and release rate of the IMP (Figure 1).

Figure 1 Two-Dimensional Design Space for the Modified Release Formulation of Capsules Filled with Minitabs



Following completion of Parts A and B, it was determined that the slowest minitab formulation provided a PK profile suitable for QD dosing but this formulation was susceptible to a food effect. Therefore, Part C of the study will investigate MR tablet formulations at up to 4 different dose levels in the fasted state. The 240 mg tablet will have a fixed composition which will have a dissolution profile similar to the slowest minitab; however, for the 360 mg and 480 mg tablets polymer compositions may be adjusted as part of a 'design space' concept to try to optimize the in vivo performance of 360 mg and /or 480 mg tablets based on the PK of the 240 mg MR tablet formulation. This adjustment will be done ahead of dosing to select a formulation at each dose unit to achieve an adjusted in vivo profile based on the PK of the 240 mg MR tablet formulation. The effect of food (standard meal) will then be investigated at either the 240 mg, 360 mg or 480 mg dose level with the option to evaluate the effect of a high fat or a delayed standard meal, to determine whether GSK2982772 can be administered with or without a food restriction in the planned proof of concept study. Although the target dosing regimen is QD, if a food effect is observed or the single dose exposure profile is not appropriate for QD dosing, BID dosing may be investigated. Dosing of multiple dose units may also be investigated.

3.2. 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].

3.3. Benefit/Risk Assessment

As of 10 November 2017, approximately 159 participants have been enrolled in 6 clinical studies with GSK2982772. In completed Study 200975, GSK2982772 was administered up to 120 mg BID for 14 days. 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.

In ongoing Phase 1 studies (high dose PK Study [205184] and MR formulation Study [205017]), a total of approximately 9 and 19 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 the ongoing Phase 2a studies in PsO Study (203167), RA (Study 203168) and Ulcerative Colitis (Study 202152), a total of approximately 64 participants have been randomised to GSK2982772 60 mg BID or 60 mg TID. . No safety concerns have been identified in the GSK2982772 development program. In Study 203167, there was a death of a 19-year-old male participant receiving GSK2982772 due to an accidental overdose with 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 participants. Therefore, all 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).

Limited reproductive toxicity studies have been conducted with GSK2982772 to date. 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 30 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 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.	**Subject Selection**: • Participants 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**: • Participants will be monitored for standard CNS-related AEs.
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended	**Subject Selection**: • Participants with recurrent, chronic or active infections

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	pharmacologic effect of GSK2982772. This may be enhanced in participants 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.	will be excluded from the study. • Participants will be screened for TB, HIV, Hepatitis B and C, and excluded from the study if positive. **Subject Monitoring**: • Participants 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 participants 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 (eg, inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (eg, risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 Investigtor'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 CO_2, oxygen saturation and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related AEs were identified.	**Subject Monitoring:** • Participants 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. 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.	**Subject Selection**: • Participants with a current history of suicidal ideation and behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Participants receiving multiple doses should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		using the C-SSRS in all participants receiving multiple doses. See Section 9.4.5.
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).	**Subject Selection**: • Male and female participants 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 30 days (females) and 90 days (males) after the last administration of study drug (Appendix 5). • Females of childbearing potential will undergo serum pregnancy test at screening and follow-up and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and OAT3 substrates were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates.	**Subject Selection:** • No concomitant medications will be permitted in this study with the exception of paracetamol/acetaminophen, hormonal contraception, hormone replacement therapy and other treatments required for AEs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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].	**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 and the medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, Labs, etc).

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize 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

Objectives	Endpoints
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each test minitab MR formulation in a capsule (120 mg) compared to the IR formulation (120 mg)	• 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 ($AUC_{(0\text{-}24)}$), area under the curve from time zero to 12 hours ($AUC_{(0\text{-}12)}$), maximum observed concentration (C_{max}), Concentration at 12 hours post-dose (C_{12h}), Concentration at 24 hours post-dose (C_{24h}) and ratio of C_{max} : C_{12h} and C_{max} : $C_{24h,}$ relative bioavailability ($Frel_{formulation}$) based on AUC and C_{max}
• To evaluate the single dose PK profile of GSK2982772 from the MR tablet (240 mg) compared to the IR formulation (240 mg)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$, C_{max}, C_{12h}, C_{24h} and ratio of C_{max} : C_{12h} and C_{max} : $C_{24h,}$ $Frel_{formulation}$ based on AUC and C_{max}
Secondary	
• To assess the impact of high fat meal on the PK of GSK2982772 following single dose administration of the selected minitab MR formulation in a capsule (120 mg)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t),}$ C_{max} and time to C_{max} (T_{max}), $Frel_{FE}$ based on AUC and C_{max}
• To determine if there are any dose dependant changes in the absorption of GSK2982772 following repeat dose	• GSK2982772 $AUC_{(0\text{-}24)}$, C_{max} and T_{max} if once daily (QD) dosing, on Day 1 and Day 3 • GSK2982772 $AUC_{(0\text{-}12)}$, $AUC_{(12\text{-}24),}$, C_{max}

Objectives	Endpoints
administration of the selected minitab MR formulation in a capsule at target daily doses of 30, 60 and 240 mg	and T_{max} after morning dose, C_{max} and T_{max} after evening dose if twice daily (BID) dosing, on Day 1 and Day 3
• To assess the impact of food on the PK of GSK2982772 following single dose administration of the MR tablet (dose corrected, as appropriate)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, or $AUC_{(0\text{-}24)}$, C_{max} and time to C_{max} (T_{max}), $Frel_{FE}$ based on AUC and C_{max} (dose corrected, as appropriate)
• To determine if there are any dose dependent changes in the absorption of GSK2982772 following single dose administration or BID dose administration of the MR tablet	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, C_{max}, C_{24h} and ratio of C_{max} : C_{24h}, and T_{max} • GSK2982772 $AUC_{(0\text{-}12)}$, C_{12h}, and ratio of C_{max} : C_{12h} if BID dosing
• To assess the safety and tolerability of single doses of GSK2982772 IR formulation and single and repeat doses of the MR formulation in a capsule, and single doses or BID doses of the MR tablet	• 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
Exploratory	
• To assess the impact of a standard meal on the PK of GSK2982772 following administration of the selected minitab MR formulation in a capsule	• GSK2982772 $AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}t)}$, C_{max}, T_{max} and $Frel_{FE}$ based on AUC and C_{max} (dose corrected as appropriate)

5. STUDY DESIGN

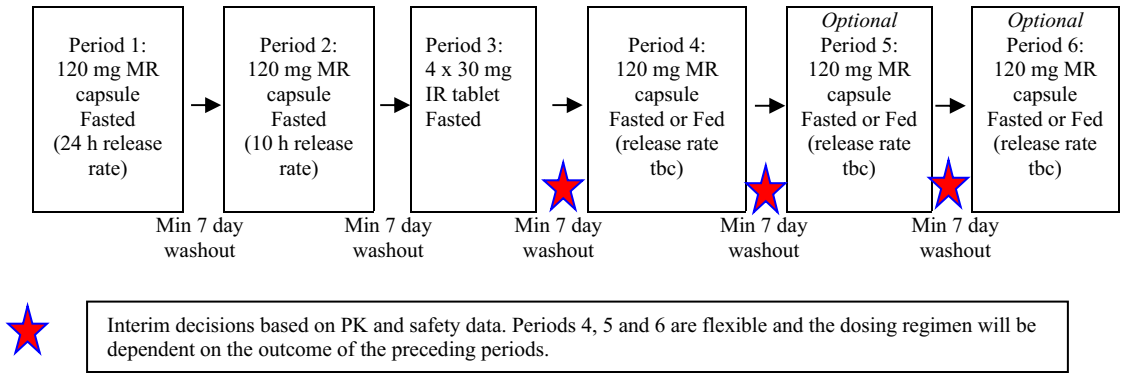
5.1. Overall Design

This is an open label, single centre, three part, single and repeat dose study in healthy male and female participants to assess MR minitab formulations of GSK2982772 in a capsule. Assuming a suitable MR minitab formulation in a capsule is identified, the impact of food (high-fat meal) on the rate and extent of absorption will be evaluated as well as an assessment of the relationship between dose and systemic exposure to GSK2982772 following repeat dosing for 3 days. MR tablet formulations of GSK2982772 will also be investigated, along with the impact of food on the rate and extent of absorption.

Part A of the study is a non-randomised 6 period, sequential, 6-way fixed sequence design in which up to 4 MR minitab formulations in a capsule may be evaluated following single dose administration in the fasted state (120 mg) (Figure 2). Periods 1, 2 and 3 will evaluate a slow MR release duration (nominally 24 hours), a fast MR release duration (nominally 10 hours), and IR tablet, 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/or to evaluate the impact of food (high-fat meal) on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 to 2.

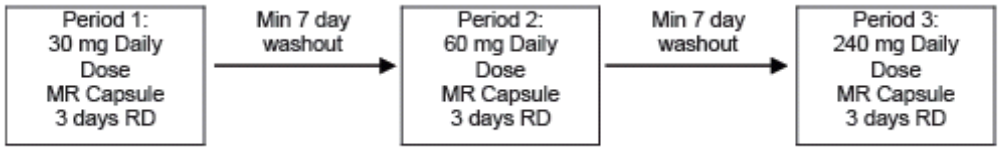
Participants will be admitted to the clinic in the morning of the day before dosing (i.e. Day -1) of each inpatient period. Each inpatient period will consist of 3 days and 2 nights followed by a minimum washout of 7 days between doses. A follow-up visit will occur at least 7 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period.

Figure 2 Part A Study Design – Formulation Optimisation and Food Effect



Part B of the study will be an open-label, repeat dose study in which the selected MR minitab formulation in a capsule will be evaluated following 3 days repeat dosing of GSK2982772 at target daily doses of 30, 60 and 240 mg (Figure 3). The target dose may be subject to change based upon evaluation of the emerging data from Part A, e.g. if the bioavailability of 120 mg MR formulation in a capsule is less than the 120 mg IR tablet (reference) formulation. In Part B, administration of the MR minitab formulation in a capsule will either be in the fasted state or with a standard meal (non-high fat), depending on the results of the food effect assessment in Part A. The prandial state for each dosing period may be selected as fasted or fed (standard meal) but within each dosing period, all doses will be administered in the same prandial state. The frequency of dosing in Part B will either be QD or BID depending on the PK profile in Part A. Whether dosing is QD or BID, the total daily doses will remain the same. If BID dosing is selected the final dose will be the evening dose of Day 3. 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 5 days and 4 nights. There will be a minimum of 7 days washout between the last morning dose of one period and the first dose of the next period. A follow-up visit will occur at least 7 days after the last study treatment.

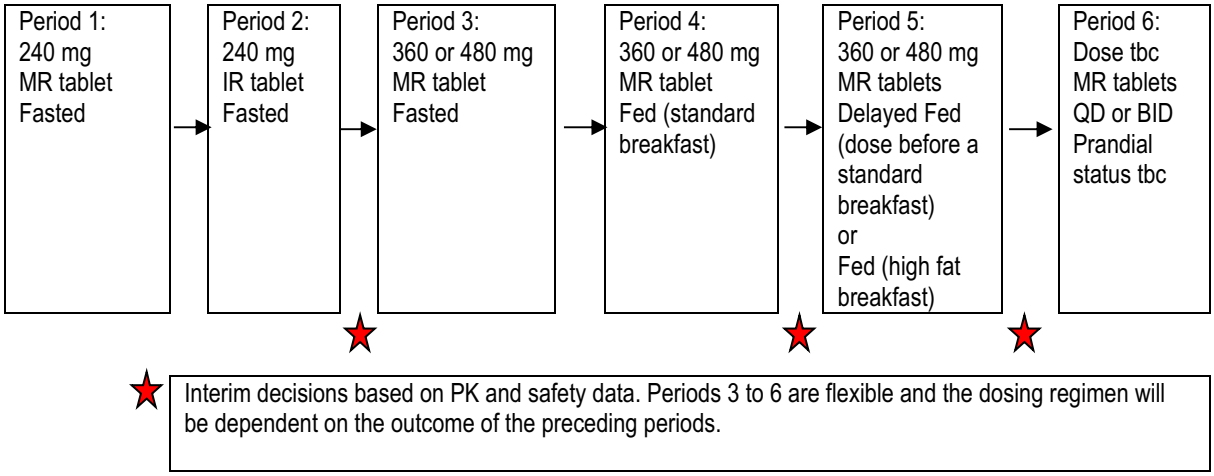
Figure 3 Part B Study Design – Dose Ranging



Part C of the study is a non-randomised 6 period, sequential, fixed sequence crossover design in which MR tablet formulations will be evaluated (Figure 4). Periods 1 and 2 will evaluate single dose administration of a 240 mg MR tablet in the fasted state and the 240 mg IR tablet (reference), respectively. Periods 3, 4, 5 and 6 will be flexible and the dosing regimen will be dependent on the outcome of Periods 1 and 2. In Periods 3 to 6, there will be the option to evaluate higher doses, the impact of a high-fat meal and/or standard meal after dosing or BID dosing.

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 3 days and 2 nights followed by a minimum washout of 7 days between doses. A follow-up visit will occur at least 7 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period (if BID dosing is selected for Period 6, participants will receive 2 doses of study treatment in this inpatient period).

Figure 4 Part C Study Design –Modified Release Tablet Formulations and Food Effect



The doses in Periods 3 to 6 may be adjusted based on results from Periods 1 and 2. The dose will not exceed the exposure observed in the high dose PK study (205184) following IR dosing of 240 mg TID.

5.1.1. Criteria for Interim Decisions

In Part A there will be an interim review following completion of Periods 1 to 3 to determine the formulation and the prandial state for Period 4. Similarly, there will be an

interim review following Periods 4 and 5. Following the final period of Part A, the formulation, doses, dosing frequency (QD or BID) and prandial state for each dosing period of Part B will be determined. However, the highest dosing regimen will be selected to ensure that the maximum daily dose will not exceed the equivalent of an IR dose of 240 mg, 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 480 mg). In Part C, there will be an interim review following completion of Periods 1 and 2 to determine the dose for Periods 3 and 4 (360 mg or 480 mg). Similarly, there will be an interim review following Periods 4 and 5 to determine dose, prandial state and and dosing regimen (QD or BID).
Interim decisions will only be made after a complete review of all relevant data collected from the previous dose group. Data must be available from a minimum of 12 participants who have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3 Part A and Period 2 Part C; IR regimen [Regimen C and Regimen K]). 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 full data, as described below, are not available for 12 participants, the principal investigator (PI), scientific lead and sponsor will take a decision as to whether the data available are sufficient to support the formulation selection decision. If data in fewer than 16 participants are used in the decision process, additional participants will not be dosed 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 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$, T_{max}, C_{max}, C_{12h}, C_{24h} and ratio of C_{max} : C_{12h} and C_{max} : C_{24h}, Frel based on AUC and C_{max} for test vs reference formulations and fed vs fasted, where relevant.
- Protocol deviations will be reviewed to ensure they have had no significant impact on the above data

The decision on formulation 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 GSK Trial Master File.

5.2. Number of Participants

In Part A, 16 healthy participants will be enrolled such that at least 12 evaluable participants complete the study. An evaluable participant will have completed the

planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen [Regimen C]). 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.

In Part B, 10 healthy participants will be enrolled such that at least 6 evaluable participants complete the study. An evaluable participant will have received all 3 days of dosing at 2 or more dose levels and completed the planned PK assessments up to 24 hours after the first dose on Day 3.

In Part C, 16 participants will be enrolled such that at least 12 evaluable participants complete the study. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 2; IR regimen). An evaluable participant must also have received the relevant test and reference formulations for the comparisons of interest e.g. the MR tablet and the IR reference at 240 mg.

Participants withdrawn due to an IMP-related AE 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 8 replacement participants may be enrolled in Part A. The maximum number of participants that may be dosed in Part A is 24.

Up to 5 replacement participants may be enrolled in Part B. The maximum number of participants that may be dosed in Part B is 15.

Up to 8 replacement participants may be enrolled in Part C. The maximum number of participants that may be dosed in Part C is 24.

Replacement participants enrolled will be dosed with the next planned treatment of the withdrawn subject, and they will not receive any treatment that the withdrawn subject has already received with the exception of the need to increase subject numbers 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 subject and the minimum washout period will be respected with regard to the timing of dosing of the IR formulation.

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 end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

Pharmacokinetic data from the FTIH study for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_03] showed that the half-life of GSK2982772 was shorter than predicted (~2 to 3 hours). As a result, BID and TID dosing regimens are being evaluated in three ongoing Phase 2a studies in psoriasis, ulcerative colitis and RA. A QD formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. Therefore, switching to a QD formulation for the Phase 2b DR studies and subsequent Phase 3 studies would be advantageous.

This current study is being conducted to evaluate the feasibility of developing an MR formulation using a minitab approach filled into a capsule. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. The total weight of the minitab will be 20 mg and between 3 and 12 minitabs can be loaded into a capsule for oral administration. Initially the PK profiles of slow (approximately 24 hours) and fast (approximately 10 hours) release rates of MR minitab will be compared to the PK profile of the IR tablet. In subsequent arms of the study, the release rate may be adapted to achieve the target PK profile. The effect of a high fat meal on the absorption of GSK2982772 when co-administered with the selected minitab MR formulation in a capsule will be evaluated to ensure that dose dumping does not occur. In addition, a range of repeat doses will be evaluated to ensure that the MR formulation in a capsule can achieve a sufficient GSK2982772 systemic exposure range to support the Phase IIb DR studies.

Part C of this study is being conducted to evaluate a MR tablet formulation of GSK2982772 that is expected to give a similar in vivo PK profile to that of the slowest minitab MR formulation from Part A. Initially, a dose of 240 mg of the MR tablet with a fixed polymer composition and similar dissolution profile to the slowest mintab formulation will be compared with the IR tablet formulation. The PK profiles of the minitab MR formulations were affected by food; therefore, the effect of a standard meal on the PK profile of GSK2982772 will also be investigated to determine if the MR tablet can be administered with or without food restrictions. Higher doses (as higher tablet strength [360 mg or 480 mg] and/or multiple dose units and/or BID dosing) will also be investigated to determine if there are any dose dependent changes in absorption. The polymer compositions of 360 mg and 480 mg tablets will be adjusted as part of a 'design space' concept to try to optimize the in vivo performance of 360 mg and /or 480 mg tablets based on the PK of the 240 mg MR tablet formulation. This adjustment will be done ahead of dosing to select a formulation at each dose unit to achieve an improved in vivo profile based on the PK of the 240 mg MR tablet formulation.

The results from the first two periods will determine the dose levels of Periods 3 and 4. In Periods 5 and 6 of the study, the dose level may be changed , the dose may be given BID, and participants may be dosed in the fasted state, following a high fat meal or before a standard meal.

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 Part A, a single dose of 120 mg will be used for the MR minitab formulations in a capsule and for the IR tablet. In Part B, it is planned to evaluate target daily doses of 30, 60 and 240 mg for 3 days. The selection of these dose levels are based on the doses being used in the ongoing Phase 2a studies (IR 60 mg BID) and the safety and PK data from the GSK2982772 FTIH study, where doses up to IR 120 mg BID for 14 days were administered.

In Part A, a single dose of 120 mg MR has been selected since this dose is anticipated to provide systemic exposure similar to the 60 mg BID regimen being used in the ongoing Phase 2a studies (assuming a relative bioavailability of 100%). In the GSK2982772 FTIH study, 120 mg of the IR formulation was well tolerated when administered as single and repeated doses (BID for 14 days). A single 120 mg dose of the MR formulation in a capsule is expected to result in lower C_{max} than for the 120 mg IR tablet, and overall systemic exposure (AUC) is expected to be similar or lower than a single 120 mg IR tablet dose.

The administration of 120 mg MR with food is expected to maintain AUC and C_{max} values within the range of values observed following 120 mg dose in the FTIH study. In the worst case scenario of dose dumping with food, 120 mg MR would have a PK profile similar to a single dose of 120 mg IR.

In Part B, the target daily MR doses of 30, 60, 240 mg reflect the approximate dose range that is planned to be taken forward into the Phase 2b DR studies. The actual dose level may be increased (by adding additional minitabs to the capsule or by giving multiple capsules) if the relative bioavailability of the selected MR at 120 mg is less than 100% compared to a 120 mg dose of the IR tablet. Taking into account the bioavailability of MR relative to IR, it is planned that the highest dose of MR to be administered will be not exceed a total daily dose equivalent to 240 mg IR (e.g. if the bioavailability of MR is 50% that of IR, the maximum daily dose of MR to be administered would be 480 mg).

In Part C, the target doses are higher than previously evaluated in Parts A and B to reflect a revised estimate of the upper limit of the dose range to be taken forward in the Phase 2b DR studies which for the IR formulation equates to 240 mg TID (720 mg/day). This IR dose regimen has been evaluated following 1 day of dosing in healthy participants in Study 205184 and was shown to be well tolerated. The highest target dose is currently 960 mg which was predicted assuming the bioavailabilty of MR tablet relative to IR is the same as observed for the slowest minitab formulation in the fasted state (Frel = 74%). The highest dose level may be adjusted based on observed relative bioavailability of the MR tablet but will not exceed the GSK2982772 systemic exposure associated with the

single day administration of 240 mg IR TID (i.e. mean AUC of 45.0 µg.h/mL and mean C_{max} of 4.3 µg/mL).

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:

   A male participant must agree to use a highly effective contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

(ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 30 days before and 30 days after the last dose of study treatment.

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. Parts A and C only: Any history of suicidal behaviour within the past 6 months or any history of attempted suicide in a participant's lifetime.
3. Part B only: Participants with current history of Suicidal Ideation Behaviour as measured using the C-SSRS or a history of attempted suicide.
4. History of clinically significant psychiatric disorders as judged by the investigator. Depression requiring treatment in the last 2 years.
5. History of herpes zoster (shingles) reactivation.
6. History or diagnosis of obstructive sleep apnoea.
7. History of a significant respiratory disorder. Childhood asthma that has fully resolved is permitted.
8. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
9. 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.
10. History of GI surgery (with exception of appendectomy).
11. History of cholecystectomy or gall stones.
12. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active.
13. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
14. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35% of total).

15. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
16. Corrected QT interval (QTc) >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

17. 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).
18. 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

19. 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.
20. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
21. 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.
22. Participants who have previously been enrolled in this study. Participants in Part A of this study are not permitted to participate in Part B. Participants in Parts A or B of this study are not permitted to participate in Part C.

Diagnostic assessments

23. Current or history of renal disease or estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation calculation <60 mL/min/1.73m^2 at screening.
24. 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.

25. An elevated C-reactive protein (CRP) outside the normal reference range.
26. Part B only: A positive anti-nuclear antibody (ANA) outside the normal reference range.
27. Confirmed positive pre-study drug/alcohol screen.
28. Positive human immunodeficiency virus (HIV) antibody test.
29. Regular use of known drugs of abuse, or history of drug or alcohol abuse in the past 5 years.

Other Exclusions

30. 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, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
31. 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).
32. 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.
33. Unwilling or unable to swallow multiple size 0-00 capsules as part of study participation.
34. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
35. Total cholesterol ≥300 mg/dL (≥7.77 millimole [mmol]/Liter [L]) or triglycerides ≥250 mg/dL (≥2.82 mmol/L).
36. Participants who are study site employees, or immediate family members of a study site or sponsor employee.

6.3. Lifestyle Restrictions

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.

  If BID dosing in the fasted state is selected for Part B or Part C Period 6, participants will be dosed in the evening approximately 12 hours after the morning dose. Meals will be provide as described above (i.e., no food will be permitted 2 hours before and 2 hours after dosing).
- For dosing after a high fat breakfast (Part A and optionally Part C) or a standard breakfast (Parts B and C), participants will be provided with a light snack 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 min, with dosing occurring 30 min after the start of breakfast. Participants should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 min after the start of breakfast. 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.

  If BID dosing administered with food is selected for Part B or Part C Period 6, participants will be dosed in the evening following a standard evening meal. Meals will be provided as described above (with evening dosing approximately 30 minutes after the start of the evening meal).
- If dosing before a standard meal is selected in Part C, 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 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.
- If drug administration in Part B is in the fasted stated, then on Day 2 when PK samples are not being collected, meals will be provided at appropriate times, i.e., a standard breakfast at approximately 2 hours post-morning dose, lunch at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post-morning dose.

- If drug administration in Part B is in the fed state, then on Day 2 when PK samples are not being collected, meals will be provided at appropriate times, i.e., a standard breakfast 30 mins prior to the morning dose, lunch at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post-morning dose.
- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, 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 (eg, 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 (Optional)	F (Optional)
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	Prototype MR Minitablet in Capsule Formulation A	Prototype MR Minitablet in Capsule Formulation B	IR Tablet Reference	Prototype MR Minitablet in Capsule Formulation A, B or C	Prototype MR Minitablet in Capsule Formulation A, B, C or D	Prototype MR Minitablet in Capsule Formulation A, B, C or D
Unit dose strength(s)/ Dosage level(s):	60 mg / 120 mg	60 mg / 120 mg	30 mg / 120 mg	60 mg / 120 mg	60 mg / 120 mg	60 mg / 120 mg
Route of Administration	Oral with 240 mL water					
Dosing instructions:	2 capsules, on the morning of Day 1 following an overnight fast	2 capsules, on the morning of Day 1 following an overnight fast	4 tablets in the morning of Day 1 following an overnight fast	2 capsules, on the morning of Day 1 following an overnight fast (if Formulation C) or following a high fat breakfast (if Formulation A or B)	2 capsules, on the morning of Day 1 following an overnight fast (if Formulation D) or following a high fat breakfast (if Formulation A, B or C)	2 capsules, on the morning of Day 1 following a high fat breakfast

Regimen	**A**	**B**	**C**	**D**	**E (Optional)**	**F (Optional)**
Packaging and Labelling	85 cc HDPE white bottle	85 cc HDPE white bottle	45 cc HDPE white bottle	85 cc HDPE white bottle	85 cc HDPE white bottle	85 cc HDPE white bottle
	Each HDPE bottle will be labelled as required per country requirement.					
Manufacturer	Quotient	Quotient	Quotient	Quotient	Quotient	Quotient

7.1.2. Treatments Administered - Part B

Regimen	**G**	**H**	**I**
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	Prototype MR Minitablet in Capsule Formulation X	Prototype MR Minitablet in Capsule Formulation X	Prototype MR Minitablet in Capsule Formulation X
Unit dose strength(s)/ Daily Dosage level(s)[a]:	15 or 30 mg / 30 mg	30 or 60 mg / 60 mg	60 mg / 240 mg
Route of Administration	Oral with 240 mL water		
Dosing instructions:	1 x 30 mg capsule in the morning of Days 1 to 3 or 1 x 15 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)	1 x 60 mg capsule in the morning of Days 1 to 3 or 1 x 30 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)	4 x 60 mg capsule in the morning of Days 1 to 3 or 2 x 60 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)
Packaging and Labelling	Study Treatment will be provided in a 85 cc HDPE white bottle. Each HDPE bottle will be labelled as required per country requirement.		
Manufacturer	Quotient		

Formulation X is the formulation selected from Part A

[a] Daily dosage levels are the anticipated dose levels for Part B; but may be subject to change depending on the results from Part A.

7.1.3. Treatments Administered - Part C

Regimen	J	K	L	M	N	O
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	MR Tablet	IR Tablet Reference	MR Tablet	MR Tablet	MR Tablet	MR Tablet
Unit dose strength(s)/ Dosage level(s):	240 mg / 240 mg	30 mg / 240 mg	360 mg / 360 mg or 480 mg / 480 mg	360 mg / 360 mg or 480 mg / 480 mg	360 mg / 360 mg or 480 mg / 480 mg	240 mg / xxx mg or 360 mg / xxx mg or 480 mg / xxx 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 a standard breakfast	1 tablet, on the morning of Day 1 following a high fat breakfast or following an overnight fast, then a standard breakfast 0.5 or 1 hour post-dose	X tablets, on the morning of Day 1, or X tablets on the morning and evening of Day 1 prandial status tbc
Packaging and Labelling	85 cc HDPE white bottle	45 cc HDPE white bottle	85 cc HDPE white bottle	85 cc HDPE white bottle	85 cc HDPE white bottle	85 cc HDPE white bottle
	Each HDPE bottle will be labelled as required per country requirement.					
Manufacturer	Quotient	GSK	Quotient	Quotient	Quotient	Quotient

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 a minimum of 12 participants in Part A, and the maximum daily dose will not exceed a total daily dose equivalent to 240 mg IR 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 480 mg).

In Part C, the maximum daily dose will not exceed a total daily dose equivalent to the systemic exposure for IR 240 mg TID (i.e. mean AUC 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 to proceed to the next dose level of GSK2982772 (either an increase or a decrease) 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 5.1.1.

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 participants 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, PPD to PPD for Part B, and PPD to PPD for Part C, using the lowest number available. Replacement participants will be assigned Subject Numbers PPD to PPD for Part A, PPD to PPD for Part B, and PPD to PPD for Part C.

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 authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized 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 (ie, 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 workbook and electronic Case Report Form (eCRF) 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

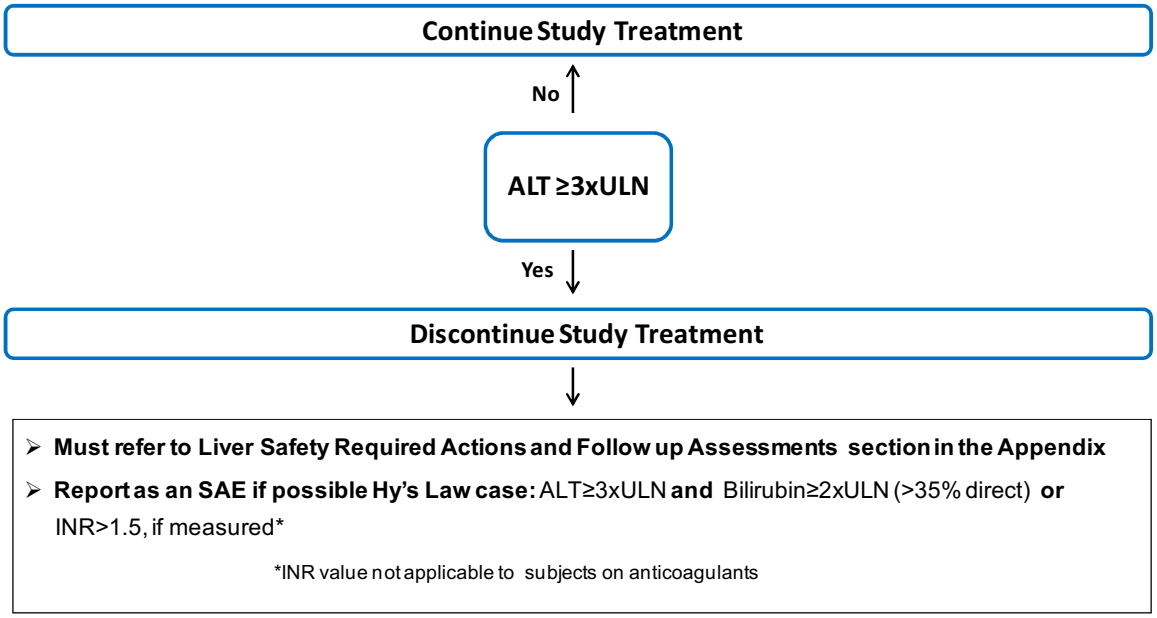
See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

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 6.

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 (e.g., 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 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, after consultation with the medical monitor, 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.

8.1.5. Rechallenge

8.1.5.1. Study Treatment Restart or Rechallenge

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

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 Case Report Form (CRF).
- 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 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 workbook.

- 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:

- The occurrence of an SAE, considered at least possibly related to the IMP administration in one participant.
- The occurrence of severe non-serious AEs considered as, at least, possibly related to the IMP administration in 2 participants at the same dose level

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 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 halted, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable, should 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 temporary suspension 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 may 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 summarized in the SoA.
- 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, 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 (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- 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 56-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 32 hours post-dose (Part A, Treatment Periods 1, 2, 4, 5, 6 and Part C, Treatment Periods 1, 3, 4, 5, 6) or 24 hours post-dose (Part A, Treatment Period 3 and Part C, Treatment Period 2) or 24 hours after the last dose (Part B Treatment Periods 1, 2 and 3; if BID dosing selected this will be after the last evening dose) 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 CRF 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, stabilized, 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 eg, 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 30 days after the last dose.
- 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 (eg, spontaneous abortion, fetal 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 CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

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 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 (e.g. 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 (e.g. 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 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:
  - The pre-dose blood sample will be taken ≤2 hours before dosing
  - 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:
  - The pre-dose urine sample will be taken ≤3 hours before dosing or the first void of the day

  - 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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which 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.
- 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 CRF.

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.

At Screening, the 'Baseline/Screening C-SSRS' will be completed in Part B only. Assessments done at pre-dose Day 1 and Day 4, the 'Since Last Visit C-SSRS' will be completed in Part B only. GSK Version 4.1 of both rating scales will be used.

Participant s who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their General Practitioner or appropriate psychiatric care and be discontinued from study medication. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 9.2). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

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

Genetics are not evaluated in this study.

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}, $AUC_{(0-inf)}$, C_{12} and C_{24} and peak to trough concentration ratio for each test minitab MR formulation in a capsule (120 mg) relative to the IR formulation (120 mg).

10.2. Sample Size Determination

10.2.1. Sample Size Determination - Part A

To date, there are no MR formulation variability data available. The maximum between-subject coefficient of variation (CV_b) for the PK parameters observed in Study 200975 following GSK2982772 capsule formulation were used for precision estimates; CV_b (%) for $AUC_{(0-inf)}$ and C_{max} for 120 mg GSK2982772 IR capsule formulation were 29.0 and 31.5 respectively. Therefore, the estimates of within subject coefficient of variation (CV_w [%]) are 20.3% and 18.8% for $AUC_{(0-inf)}$ and C_{max}, respectively. 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 15.3% and 14.2% of the point estimate respectively.

Since it is expected that the MR formulation is to reduce the C_{max} by 50% whilst maintaining the AUC, a sample size of 12 ensures that the 90% CI is within the region 0.8-1.25 for AUC and 0.4-0.625 for C_{max}, if the observed geometric ratio is 0.93-1.08 for AUC and 0.47-0.54 for C_{max}.

Sample Size Sensitivity – Part A

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability observed in Study 200975, the precision of these estimates calculated as half width of a 90% confidence interval for the mean ratio (MR/IR) and expressed as distance from mean to limits for 10, 12, 14 and 16 participants has been calculated (Table 5).

Table 5 Precision Estimate of Mean – Part A

CVw (%)	Precision of Mean (%)			
	N=10	N=12	N=14	N=16
15	12.70	11.30	10.30	9.50
18.8	16.00	14.20	12.90	11.90
20	17.30	15.30	13.90	12.90

For example, based upon the estimate of variability (CV_w%) of 20 and a sample size of 14, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 13.9% of the point estimate.

10.2.2. Sample Size Determination - Part B

No repeat dose MR formulation variability data are currently available. Therefore, the maximum CV_b for the PK parameters were observed in the study 200972 following repeat dose of GSK2982772 capsule formulation; CV_b (%) for $AUC_{(0-\tau)}$ and C_{max} for 20mg QD GSK2982772 IR capsule formulation on Day 1 is 36.1 and 27.1 respectively. Therefore, the estimates of equivalent CV_w (%) are 23.2 and 17.6 for C_{max} and $AUC_{(0-\tau)}$ respectively. Based on these estimates of variability and a sample size of 8 completers, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of $AUC_{(0-\tau)}$ and C_{max} will be within approximately 12.1% and 16.7% of the point estimate respectively.

Sample Size Sensitivity – Part B

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability, the precision of these estimates calculated as half width of a 90% confidence interval for the mean and expressed as distance from mean to limits for 4, 6, 8 and 10 participants has been calculated (Table 6).

Table 6 Precision Estimate of Mean – Part B

CV_b (%)	Precision of Mean (%)			
	N=4	N=6	N=8	N=10
18.4%	23.6	16.0	12.8	11.0
19.3%	25.1	16.9	13.6	11.6
24.4%	32.6	21.8	17.4	14.9
25.5%	34.2	22.8	18.2	15.6

For example, based upon the estimate of variability (CV_b%) of 19.3 and a sample size of 4, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 25.1% of the point estimate.

10.2.3. Sample Size Determination - Part C

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 $AUC_{(0\text{-inf})}$ and C_{max} were 48.7% and 58.5%, respectively. Therefore, the estimates of within-subject coefficient of variation (CV_w [%]) are 30.9% and 36.7% for $AUC_{(0\text{-inf})}$ and C_{max}, respectively. 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% 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.

Since it is expected that the MR tablet formulation is to reduce the C_{max} by 50% whilst maintaining the AUC, a sample size of 12 ensures that the 90% CI is within the region 0.748-1.342 for AUC and 0.364-0.698 for C_{max}, if the observed geometric ratio is 0.93-1.08 for AUC and 0.47-0.54 for C_{max}.

Sample Size Sensitivity – Part C

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% CI for the mean ratio (MR/IR) and expressed as distance from mean to limits for 10, 12, 14 and 16 participants has been calculated (Table 7).

Table 7 Precision Estimate of Mean – Part C

CVw (%)	Precision of Mean (%)			
	N=10	N=12	N=14	N=16
30.9	27.5	24.3	22.0	20.3
36.7	33.1	29.2	26.4	24.3

For example, based upon the estimate of variability (CV_w%) of 30.9 and a sample size of 14, it is estimated that the lower and upper bounds of the 90% CI for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 22.0% of the point estimate.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants	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 Participants 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 all parts of the study, plasma GSK2982772 concentration-time data will be analysed by non-compartmental methods.

In Parts A and C, from 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 12 hours and 24 hours post-dose (C_{12h} and C_{24h}).
- area under the plasma concentration vs time curve ($AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-12)}$ and $AUC_{(0-inf)}$).
- the percentage of AUC extrapolated beyond the last measured time point (AUC%extrap).
- terminal half-life ($t_{1/2}$).
- C_{max} to C_{12h} and C_{max} to C_{24h} ratios.
- relative bioavailability ($Frel_{formulation}$) of test formulations 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 vs fasted based on AUC and $C_{max.}$

In Part B, from the plasma concentration-time data for each of the regimens, the following PK parameters will be determined, for Day 1 and Day 3, as data permit:

- maximum observed plasma concentration (C_{max}) for QD dosing. If BID dosing, C_{max} after morning dose and evening dose.
- time to C_{max} (T_{max}) for QD dosing. If BID dosing, T_{max} after morning dose and evening dose.
- observed concentration at 12 hours and 24 hours post-dose (C_{12h} and C_{24h}).
- area under the plasma concentration-time curve ($AUC_{(0-24)}$) for QD dosing. If BID dosing, $AUC_{(0-12)}$ and $AUC_{(12-24)}$.
- C_{max} to C_{12} and C_{max} to C_{24} ratios.
- Dose normalised C_{max}, C_{12h}, C_{24h}, $AUC_{(0-tau)}$ (for BID dosing), $AUC_{(0-24)}$ and $AUC_{\mathbf{(0-inf)}}$.
- Relative bioavailability ($Frel_{FE}$) of fed (non-high fat meal) vs fasted based on AUC and C_{max} (dose corrected as appropriate)

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 loge-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. Ratio of $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}24)}$, ($AUC_{(0\text{-}t)}$, if $AUC_{(0\text{-}inf)}$ cannot be derived), C_{max}, C_{12} and C_{24} for MR formulation to IR formulation will be computed with 90% CI. C_{max} to C_{12h} and C_{max} to C_{24h} ratio for each MR formulation (120 mg or 240 mg) and the corresponding total dose of IR formulation (120 mg or 240 mg) will be computed with 90% CI.
Secondary	The secondary endpoints for food effect will be summarised descriptively. In addition, log-transformed $AUC_{(0\text{-}inf)}$ ($AUC_{(0\text{-}t)}$, if $AUC_{(0\text{-}inf)}$ cannot be derived), C_{12h}, 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 be computed for the differences for each GSK2982772 MR formulation (120 mg, 240 mg, 360 mg or 480 mg) taken in the fed state (test) vs the same dose 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 each 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	Part B, the secondary PK endpoints for the selected MR formulation at target daily doses of 30, 60 and 240 mg will be summarised descriptively. Part C, the secondary PK endpoints MR at target daily doses of 240 mg, 360 mg, 480 mg and high dose selected in Period 6 will be summarised descriptively. For Part B and Part C, plots of dose vs dose normalised $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$ ($AUC_{(12\text{-}24)}$ BID dosing), C_{12h}, C_{24h} and C_{max} (after morning and evening doses if BID dosing) will be generated to determine if there are any dose dependent changes in the absorption of GSK2982772 following repeat dose administration of the selected minitab MR formulation.
Exploratory	Part B, the exploratory endpoints for non-high fat meal food effect will be summarised descriptively and modelled as specified for the secondary food effect endpoints.

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 Participants 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 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 of preceding periods. There will be the option to either optimise the MR release duration and/or to evaluate the impact of food on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 2.

There will be an interim review following final period of Part A to determine the formulation, doses, dosing frequency (QD or BID) and prandial state for each dosing period of Part B. The data will be sent to the sponsor by Quotient, from which the decision on formulation 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, CPMS and GCSP). The decision will be documented and signed by the PI as per Quotient Sciences current SOP. Evidence of the decision will be retained in the ISF and GSK Trial Master File.

There will be no interim analysis during Part B of the study.

In Part C, there will be an interim review following completion of Periods 1 and 2 to determine the dose to be used in Periods 3 and 4. A further interim analysis after Period 4 will be used to determine if dosing should be before a standard meal (i.e., delayed standard meal) or after high fat meal in Period 5. There will be a final interim review after Period 5 to determine the dose and food status for Period 6.

See Section 5.1.1 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 or if the PK profiles indicate that a QD or BID dosing regimen isn't feasible. 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.

- Administration of MR with a high-fat meal shows dose dumping

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
AST	Aspartate Aminotransferase
AUC	Area under the concentration vs time curve
$AUC_{(0-12)}$,	Area under the curve from time zero to 12 hours
$AUC_{(0-24)}$	Area under the curve from time zero to 24 hours
$AUC_{(0-t)}$	Area under the curve from time zero to the last measurable concentration
BID	Twice daily
BUN	Blood Urea Nitrogen
C_{12}	Concentration at 12 h post-dose
C_{24}	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
CPMS	Clinical Pharmacokinetics Modelling and Simulation
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CV_b	Between subject coefficient of variation
CV_w	Within subject coefficient of variation
DR	Dose ranging
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FTIH	First time in human
Frel	Relative bioavailability
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice

HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human Chorioninc Gonadotropin
HIV	Human immunodeficiency virus
HIPPA	Health Insurance Portability and Accountability Act
HRT	Hormonal Replacement Therapy
ICF	Informed consent form
IEC	Independent Ethics Committees
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Immediate release
IRB	Institutional Review Board
ISF	Investigator site file
IVIVT	In Vitro/In Vivo Translation
L	Litre
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
mg	milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
mins	Minutes
mL	Millilitres
mmol	Millimole
MR	Modified release
MSDS	Material Safety Data Sheet
msec	Milliseconds
NOAEL	No observed adverse effect level
Pgp	P-glycoprotein
PI	Principal investigator
PIS	Participant Information Sheet
PK	Pharmacokinetic(s)
ppm	Parts per million
PsO	Plaque psoriasis
PSRAE	Possible Suicidality Related Adverse Event
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
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}
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
NONE

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12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 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 8 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	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • 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], and hepatitis C virus antibody) at screening only • Tuberculosis test (QuantiFERON) at screening only • C-reactive protein (CRP) at screening only • Anti-nuclear antibody (ANA) in Part B only The results of each test must be entered into the CRF.

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 6 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 Governance 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 workbook 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 workbook 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 authorized 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 authorized 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 CRF 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 CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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 source data verification to confirm that data entered into the CRF by authorized 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 reported on the CRF or entered in the eCRF 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 last visit of the last participant (eg follow-up assessment). 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 <u>Meeting</u> 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 <u>NOT</u> 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 jeopardize 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 CRF (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 CRF page. • 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 utilized 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 recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within 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 eCRF (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 eCRF. • 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)

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

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-hormonal 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.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- Refrain from donating sperm for duration of study and for 3 months after study completion or from last dose.
- As there is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male participants, a condom should be used by all male participants during the protocol-defined time frame in Section 6.1.

Female participants

Female participants who are not of childbearing potential do not need to use any methods of contraception.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *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
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If*

not, an additional highly effective method of contraception should be used.)
Sexual abstinence (*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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing will be performed at admission to each study period and at the follow-up visit
- 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 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 CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

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 participants 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 Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize 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 participants with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants 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 participants 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 CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

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

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.

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

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: Protocol Amendment History

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

Amendment 01 *18-Sep-2017*

Overall Rationale for the Amendment: Changes in response to MHRA feedback.

Section # and Name	Description of Change	Brief Rationale
2, Schedule of Activities	Wording amended in paragraph 3.	MHRA requested clarification that any changes in safety monitoring will require regulatory approval in the form of a substantial amendment.

TITLE PAGE

Protocol Title: A two part, non-randomised, open label study designed to assess the pharmacokinetics of GSK2982772 following administration of modified release formulations in capsule relative to an immediate release reference tablet formulation (Part A) and the pharmacokinetics of escalating, repeat doses of a selected modified release prototype (Part B) in healthy subjects

Protocol Number: 205017/01

Short Title: A study to compare the pharmacokinetics of GSK2982772 following administration of different modified release formulations in capsule relative to an immediate release tablet formulation and to investigate the pharmacokinetics of a selected modified release formulation in capsule following repeat doses for 3 days.

Compound Number: GSK2982772

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 2017-000652-25

Approval Date: 18-SEP-2017

SPONSOR SIGNATORY:

PPD

Sept 18th 2017

Date

Vice President & Head Unit Physician
Immunoinflammation Therapy Area

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 01	*18-Sep-2017*
Original Protocol	*07-Jul-2017*

Amendment 01 18-September-2017

Overall Rationale for the Amendment: Changes in response to MHRA feedback.

Section # and Name	Description of Change	Brief Rationale
2, Schedule of Activities	Wording amended in paragraph 3.	MHRA requested clarification that any changes in safety monitoring will require regulatory approval in the form of a substantial amendment.

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1. SYNOPSIS

Protocol Title: A two part, non-randomised, open label study designed to assess the pharmacokinetics of GSK2982772 following administration of modified release formulations in capsule relative to an immediate release reference tablet formulation (Part A) and the pharmacokinetics of escalating, repeat doses of a selected modified release prototype (Part B) in healthy subjects.

Short Title: A study to compare the pharmacokinetics of GSK2982772 following administration of different modified release formulations in capsule relative to an immediate release tablet formulation and to investigate the pharmacokinetics of a selected modified release formulation in capsule following repeat doses for 3 days.

Rationale: The purpose of this study is to evaluate a modified release (MR) formulation of GSK2982772 using a minitab approach filled into a capsule in order to develop a more convenient once daily (QD) dosing formulation. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. Initially, the pharmacokinetic (PK) profiles of slow (approximately 24 hours) and fast (approximately 10 hours) release rates of MR minitab will be compared to the PK profile of the immediate release (IR) tablet. In subsequent arms of the study, the release rate may be adapted to achieve the target PK profile. The effect of a high fat meal on the absorption of GSK2982772 when co-administered with the selected minitab MR formulation will be evaluated to ensure that dose dumping does not occur. In addition, the PK profile of repeat doses at 3 dose levels will be evaluated to ensure that the MR formulation can achieve a sufficient GSK2982772 systemic exposure range to support the Phase IIb dose ranging (DR) studies.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each test MR formulation in a capsule (120 mg) compared to the IR formulation (120 mg)	• 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 ($AUC_{(0\text{-}24)}$), area under the curve from time zero to 12 hours ($AUC_{(0\text{-}12)}$), maximum observed concentration (C_{max}), Concentration at 12 hours post-dose (C_{12h}), Concentration at 24 hours post-dose (C_{24h}) and ratio of C_{max} : C_{12h} and C_{max} : C_{24h}, relative bioavailability ($FrelI_{formulation}$) based on AUC and C_{max}
Secondary	
• To assess the impact of high fat meal on the PK of GSK2982772 following single dose administration of the selected MR formulation in a capsule (120 mg)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max} and time to C_{max} (T_{max}), $FrelI_{FE}$ based on AUC and C_{max}
• To determine if there are any dose dependant changes in the absorption of GSK2982772 following repeat dose administration of the selected MR formulation in a capsule at target daily doses of 30, 60 and 240 mg	• GSK2982772 $AUC_{(0\text{-}24)}$, C_{max} and T_{max} if once daily (QD) dosing, on Day 1 and Day 3 • GSK2982772 $AUC_{(0\text{-}12)}$, $AUC_{(12\text{-}24)}$,, C_{max} and T_{max} after morning dose, C_{max} and T_{max} after evening dose if twice daily (BID) dosing, on Day 1 and Day 3
• To assess the safety and tolerability of single doses of GSK2982772 IR formulation and single and repeat doses of the MR formulation in a capsule	• 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

Overall Design:

This is an open label, single centre, two part, single and repeat dose study in healthy male and female participants to assess MR minitab formulations of GSK2982772 in a capsule. Assuming a suitable MR minitab formulation in a capsule is identified, the impact of food (high-fat meal) on the rate and extent of absorption will be evaluated as well as an assessment of the relationship between dose and systemic exposure to GSK2982772 following repeat dosing for 3 days.

Part A of the study is a non-randomised 6 period, sequential, 6-way fixed sequence design in which up to 4 MR minitab formulations in a capsule may be evaluated following single dose administration in the fasted state (120 mg). Periods 1, 2 and 3 will evaluate a slow MR release duration (nominally 24 hours), a fast MR release duration (nominally 10 hours), and IR tablet, 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/or to evaluate the impact of food (high-fat meal) on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 2.

Part B of the study will be an open-label, repeat dose study in which the selected MR minitab formulation in a capsule will be evaluated following 3 days repeat dosing of GSK2982772 at target daily doses of 30, 60 and 240 mg. In Part B, administration of the MR minitab formulation in a capsule will either be in the fasted state or with a standard meal (non-high fat), depending on the results of the food effect assessment in Part A. The frequency of dosing in Part B will either be QD or BID depending on the PK profile in Part A. Whether dosing is QD or BID, the total daily doses will remain the same.

Number of Participants:

Sixteen participants will be enrolled into Part A of the study to allow for the completion of at least 12 evaluable participants. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen). 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.

Ten participants will be enrolled into Part B of the study to allow for the completion of at least 6 evaluable participants. An evaluable participant will have received all 3 doses and completed the planned safety and PK assessments up to 24 hours after the last dose.

Treatment Groups and Duration:

In Part A, each participant will be enrolled in the study for approximately 8 to 13 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 will consist of 3 days and 2 nights followed by a minimum washout of 7 days between doses.

A follow-up visit will occur at least 7 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 9 weeks. Participation will include a screening evaluation within 28 days of study treatment administration and 3 separate 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 will consist of a 5 day, 4-night inpatient period with a minimum of 7 days washout between the last morning dose of one period and the first dose of the next period. A follow-up visit will occur at least 7 days after the last study treatment.

2. SCHEDULE OF ACTIVITIES (SOA)

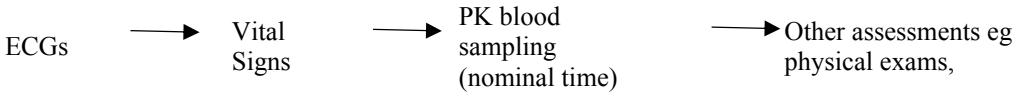
The schedules of activities for Part A and Part B are presented in Table 1 and Table 3, respectively. The time points for the PK blood sample collection in Part A and Part B are presented in Table 2 and Table 4, respectively.

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 pharmacokinetic 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:



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 Part A

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2		
Informed consent	X					
Inclusion and exclusion criteria[1]	X					1. Recheck clinical status before 1st dose of study medication.
Demography	X					
Demonstrate ability to swallow size 0-00 capsules	X					
Full physical examination including height and weight	X					
Brief physical examination		X		X[2]	X	2. Discharge (32 h post-dose for Treatment Period 1, 2, 4, 5 and 6 24 h post-dose for Treatment Period 3)
Medical history (includes substance usage)[3]	X					3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X					
Follicle Stimulating Hormone (FSH) (as needed in women of non-childbearing potential only)	X					
Serum pregnancy test (WOCBP only)	X				X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2		
Urine pregnancy test (WOCBP only)		X				
Human Immunodefeciency Virus (HIV), Hepatitis B and C screening[4]	X					4. 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	X[5]	X[5]	X	5. Pre-dose (Treatment Period 1 only) and 24 h post-dose Allowable windows in Section 9.4.4
Glomerular filtration rate	X					
C-reactive protein (CRP)	X					
12-lead ECG	X[6]	X	X[7]	X[8]	X	6. In triplicate 7. Pre-dose and 2 and 12 h post-dose 8. 24 h post-dose Allowable windows in Section 9.4.3

Procedure	**Screening (up to 28 days before Day 1)**	**Treatment Period 1, 2, 3, 4, 5, 6 Day**			**Follow-up/Study Discontinuation (7 days post last dose)**	**Notes**
		–1	**1**	**2**		
Vital signs	X	X	X[9]	X[10]	X	9. Pre-dose and 2 and 12 h post-dose 10. 24 h post-dose Allowable windows in Section 9.4.2
Study treatment			X			
AE review		←==========		==========→	X	
Serious AE (SAE) review	X	←==========		==========→	X	
Concomitant medication review		←==========		==========→	X	
PK blood sample collection			X[11]	X[11]		11. Time points in Table 2

Table 2 Pharmacokinetic Blood Sample Collection Times – Part A

	Treatment Periods 1, 2, 4, 5 and 6 (MR Formulations)																	
Time (h)	**Pre-dose**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**
Dosing		X																
PK sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

Table 3 Schedule of Activities for Part B

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
Informed consent	X							
Inclusion and exclusion criteria[1]	X							1. Recheck clinical status before 1st dose of study medication.
Demography	X							
Demonstrate ability to swallow size 0-00 capsules	X							
Full physical examination including height and weight	X							
Brief physical examination		X				X[2]	X	2. Discharge (24 h after the last dose)
Medical history (includes substance usage)[3]	X							3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X							
FSH (as needed in women of non-childbearing potential only)	X							
Serum pregnancy test (WOCBP only)	X						X	
Urine pregnancy test (WOCBP only)		X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
HIV, Hepatitis B and C screening[4]	X							4. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Tuberculosis 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	X[5]			X[6]	X	5. Pre-dose 6. 24 h after the last dose Allowable windows in Section 9.4.4
Glomerular filtration rate	X							
CRP	X							
ANA	X					X[7]		7. 24 h after the last dose

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
12-lead ECG	X[8]	X	X[9]	X[10]	X[9]	X[11]	X	8. In triplicate 9. Pre-dose and 2 and 12 h post-dose 10. Pre-dose 11. 24 h after the last dose Allowable windows in Section 9.4.3 Time points may be subject to change depending on results from Part A
Vital signs	X	X	X[12]	X[13]	X[12]	X[14]	X	12. Pre-dose and 2 and 12 h post-dose 13. Pre-dose 14. 24 h after the last dose Allowable windows in Section 9.4.2 Time points may be subject to change depending on results from Part A
Columbia Suicide Risk questionnaire	X		X[15]			X[16]		15. Pre-dose 16. 24 h after last dose of each period
Study treatment			X	X	X			
AE review		←==========				==========→	X	
SAE review	X	←==========				==========→	X	
Concomitant medication review		←==========				==========→	X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
PK blood sample collection			X[17]	X[17]	X[17]	X[17]		17. Time points in Table 4

Table 4 Pharmacokinetic Blood Sample Collection Times – Part B

	Periods 1, 2 and 3													
	Days 1 and 3													
Time (h)	**Pre-dose**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Dosing[a]		X												
PK sampling[b]	X		X	X	X	X	X	X	X	X	X	X	X	X[c]

[a] Subjects will be dosed on Days 1, 2 and 3; however, no PK samples will be taken post-dose on Day 2

[b] PK sampling schedule may be amended based upon the PK data from Part A and/or if BID dosing is selected for Part B. If BID dosing is employed the number of PK samples may be reduced i.e. some of the samples between 14 and 24 h may not be required. In addition, the 12 h sample will be taken prior to administering the second daily dose.

[c] Day 1 24 h post-dose sample should be taken prior to dosing on Day 2.

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. Study Rationale

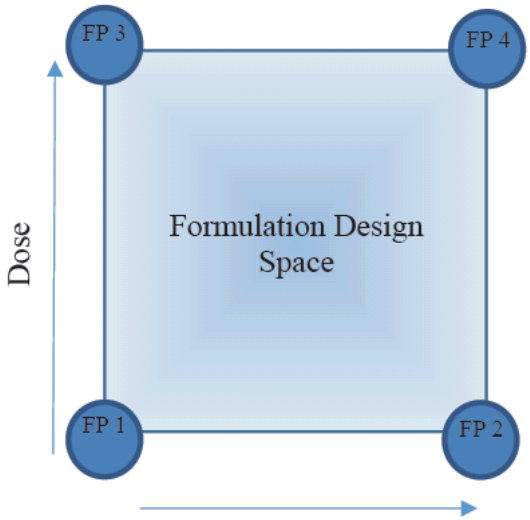
Pharmacokinetic data from the first time in human (FTIH) study for GSK2982772 (200975) [GlaxoSmithKline Document Number 2014N204126_02] showed that the half-life of GSK2982772 was short (~2 to 3 hours). As a result, BID and three times daily (TID) dosing regimens are being evaluated in three ongoing proof of mechanism studies. A QD formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. This current study is being conducted to evaluate the feasibility of developing an MR formulation using a minitab approach filled into a capsule. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. In addition, the number of minitabs included in the capsule can be varied to adjust the dose.

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 Clinical (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.

There will be the option to test a range of formulations based on a 2-dimensional design space describing the dose level and release rate of the IMP (Figure 1).

Figure 1 Two-Dimensional Design Space for the Modified Release Formulation



3.2. 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_02].

3.3. Benefit/Risk Assessment

To date, approximately 124 participants have been enrolled in 4 clinical studies with GSK2982772. In Study 200975, GSK2982772 was administered up to 120 mg BID for 14 days. A total of 67 participants received GSK2982772 and 26 participants received placebo (including crossover) in that study. In the ongoing Phase 2a studies in PsO Study (203167), RA (Study 203168) and Ulcerative Colitis (Study 202152), a total of approximately 26 participants have been randomised to GSK2982772 60 mg BID. Overall, GSK2982772 has been generally well tolerated and no drug-related SAEs have been reported. In Study 203167, there was a death of a 19-year-old male participant due to an accidental overdose with 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 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).

Limited reproductive toxicity studies have been conducted with GSK2982772 to date. 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 30 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. **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_02]. No drug-associated CNS AEs were identified and no SAEs were reported.	**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.
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids.	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, HIV, Hepatitis B and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: In the FTiH study, no SAEs were reported. One subject experienced an Adverse Effect (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded Investigator determined this to be potentially drug-related.	C, and excluded from the study if positive. **Subject Monitoring**: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 8.1.3).
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (eg, inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (eg, risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
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 Investigtor's	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related AEs. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Brochure for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02]. **Clinical data**: In the FTIH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO_2, oxygen saturation and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related AEs were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based upon pre-clinical studies. **Clinical data**: In the FTIH study, there have been some reports of lethargy, abnormal dreams, and depressed mood. No events of suicidal ideation or behaviour or changes in behaviour were reported.	**Subject Selection**: • Subjects with a current history of suicidal ideation and behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Subjects receiving multiple doses should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel using the C-SSRS in all subjects receiving multiple doses. See Section 9.4.5.
Reproductive toxicity	**Non-clinical data:** In an early rat embryofoetal development study, there was no maternal or developmental toxicity at doses ≤200 mg/kg/day. In a rabbit embryofoetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection**: • Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for 30 days before first administration of study drug until 30 days (females) and 90 days (males) after the last administration of study drug (Appendix 5). • Females of childbearing potential will undergo serum pregnancy test at screening and follow-up and then

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and OAT3 substrates were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. 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_02].	**Subject Selection:** • No concomitant medications will be permitted in this study with the exception of 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 and the medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, Labs, etc).

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize 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

Objectives	Endpoints
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each test MR formulation in a capsule (120 mg) compared to the IR formulation (120 mg)	• 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 ($AUC_{(0\text{-}24)}$), area under the curve from time zero to 12 hours ($AUC_{(0\text{-}12)}$), maximum observed concentration (C_{max}), Concentration at 12 hours post-dose (C_{12h}), Concentration at 24 hours post-dose (C_{24h}) and ratio of C_{max} : C_{12h} and C_{max} : C_{24h}, relative bioavailability ($FreI_{formulation}$) based on AUC and C_{max}
Secondary	
• To assess the impact of high fat meal on the PK of GSK2982772 following single dose administration of the selected MR formulation in a capsule (120 mg)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, C_{max} and time to C_{max} (T_{max}), $FreI_{FE}$ based on AUC and C_{max}
• To determine if there are any dose dependant changes in the absorption of GSK2982772 following repeat dose administration of the selected MR formulation in a capsule at target daily doses of 30, 60 and 240 mg	• GSK2982772 $AUC_{(0\text{-}24)}$, C_{max} and T_{max} if once daily (QD) dosing, on Day 1 and Day 3 • GSK2982772 $AUC_{(0\text{-}12)}$, $AUC_{(12\text{-}24)}$,, C_{max} and T_{max} after morning dose, C_{max} and T_{max} after evening dose if twice daily (BID) dosing, on Day 1 and Day 3
• To assess the safety and tolerability of single doses of GSK2982772 IR formulation	• Adverse events (AEs)

Objectives	Endpoints
and single and repeat doses of the MR formulation in a capsule	• 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

5. STUDY DESIGN

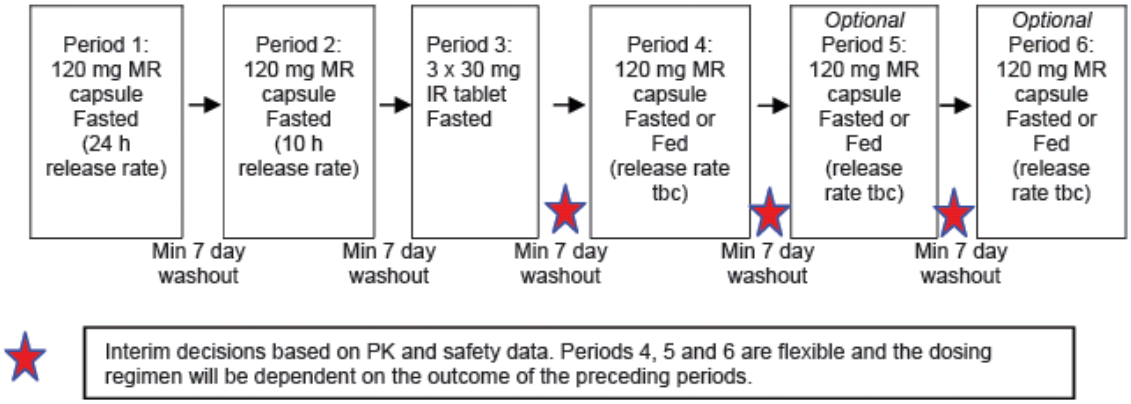
5.1. Overall Design

This is an open label, single centre, two part, single and repeat dose study in healthy male and female participants to assess MR minitab formulations of GSK2982772 in a capsule. Assuming a suitable MR minitab formulation in a capsule is identified, the impact of food (high-fat meal) on the rate and extent of absorption will be evaluated as well as an assessment of the relationship between dose and systemic exposure to GSK2982772 following repeat dosing for 3 days.

Part A of the study is a non-randomised 6 period, sequential, 6-way fixed sequence design in which up to 4 MR minitab formulations in a capsule may be evaluated following single dose administration in the fasted state (120 mg) (Figure 2). Periods 1, 2 and 3 will evaluate a slow MR release duration (nominally 24 hours), a fast MR release duration (nominally 10 hours), and IR tablet, 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/or to evaluate the impact of food (high-fat meal) on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 to 2.

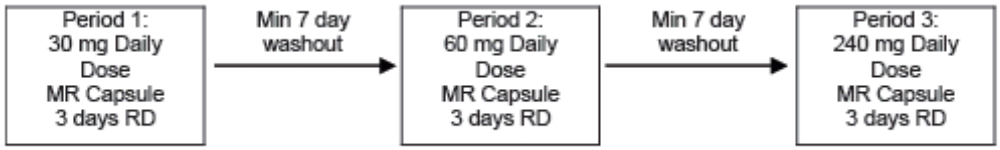
Subjects will be admitted to the clinic in the morning of the day before dosing (i.e. Day -1) of each inpatient period. Each inpatient period will consist of 3 days and 2 nights followed by a minimum washout of 7 days between doses. A follow-up visit will occur at least 7 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period.

Figure 2 Part A Study Design – Formulation Optimisation and Food Effect



Part B of the study will be an open-label, repeat dose study in which the selected MR minitab formulation in a capsule will be evaluated following 3 days repeat dosing of GSK2982772 at target daily doses of 30, 60 and 240 mg (Figure 3). The target dose may be subject to change based upon evaluation of the emerging data from Part A, e.g. if the bioavailability of 120 mg MR formulation in a capsule is less than the 120 mg IR tablet (reference) formulation. In Part B, administration of the MR minitab formulation in a capsule will either be in the fasted state or with a standard meal (non-high fat), depending on the results of the food effect assessment in Part A. The frequency of dosing in Part B will either be QD or BID depending on the PK profile in Part A. Whether dosing is QD or BID, the total daily doses will remain the same. If BID dosing is selected the final dose will be the evening dose of Day 3. 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 will consist of 5 days and 4 nights. There will be a minimum of 7 days washout between the last morning dose of one period and the first dose of the next period. A follow-up visit will occur at least 7 days after the last study treatment.

Figure 3 Part B Study Design – Dose Ranging



5.1.1. Criteria for Interim Decisions

In Part A there will be an interim review following completion of Periods 1 to 3 to determine the formulation and the prandial state for Period 4. Similarly, there will be an interim review following Periods 4 and 5. Following the final period of Part A, the formulation, doses, dosing frequency (QD or BID) and prandial state for Part B will be determined. However, the highest dosing regimen will be selected to ensure that the maximum daily dose will not exceed the equivalent of an IR dose of 240 mg, 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 480 mg). Interim

decisions will only be made after a complete review of all relevant data collected from the previous dose group. Data must be available from a minimum of 12 participants who have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen [Regimen C]). 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 full data, as described below, are not available for 12 participants, the principal investigator (PI), scientific lead and sponsor will take a decision as to whether the data available are sufficient to support the formulation selection decision. If data in fewer than 16 participants are used in the decision process, additional participants will not be dosed to increase the number of participants in the completed regimen.

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

- AEs, vital signs, ECGs, safety laboratory data and physical examinations.
- Plasma concentrations of GSK2982772.
- PK parameter estimates GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$, T_{max}, C_{max}, C_{12h}, C_{24h} and ratio of C_{max} : C_{12h} and C_{max} : C_{24h}, Frel based on AUC and C_{max} for test vs reference formulations and fed vs fasted, where relevant.
- Protocol deviations will be reviewed to ensure they have had no significant impact on the above data

The decision on formulation 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 Clinical current standard operating procedure (SOP). Evidence of the decision will be retained in the Investigator Site File (ISF) and GSK Trial Master File.

5.2. Number of Participants

In Part A, 16 healthy participants will be enrolled such that at least 12 evaluable participants complete the study. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen [Regimen C]). 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.

In Part B, 10 healthy participants will be enrolled such that at least 6 evaluable participants complete the study. An evaluable participant will have received all 3 days of dosing at 2 or more dose levels and completed the planned PK assessments up to 24 hours after the first dose on Day 3.

Participants withdrawn due to an IMP-related AE 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 8 replacement participants may be enrolled in Part A. The maximum number of participants that may be dosed in Part A is 24.

Up to 5 replacement participants may be enrolled in Part B. The maximum number of participants that may be dosed in Part B is 15.

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

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 end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

Pharmacokinetic data from the FTIH study for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02] showed that the half-life of GSK2982772 was shorter than predicted (~2 to 3 hours). As a result, BID and TID dosing regimens are being evaluated in three ongoing Phase 2a studies in psoriasis, ulcerative colitis and RA. A QD formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. Therefore, switching to a QD formulation for the Phase 2b DR studies and subsequent Phase 3 studies would be advantageous.

This current study is being conducted to evaluate the feasibility of developing an MR formulation using a minitab approach filled into a capsule. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. The total weight of the minitab will be 20 mg and between 3 and 12 minitabs can be loaded into a capsule for oral administration. Initially the PK profiles of slow (approximately 24 hours) and fast (approximately 10 hours) release rates of MR minitab will be compared to the PK profile of the IR tablet. In subsequent arms of the study, the release rate may be adapted to achieve the target PK profile. The effect of a high fat meal on the absorption of GSK2982772 when co-administered with the selected

minitab MR formulation in a capsule will be evaluated to ensure that dose dumping does not occur. In addition, a range of repeat doses will be evaluated to ensure that the MR formulation in a capsule can achieve a sufficient GSK2982772 systemic exposure range to support the Phase IIb DR studies.

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 Part A, a single dose of 120 mg will be used for the MR minitab formulations in a capsule and for the IR tablet. In Part B, it is planned to evaluate target daily doses of 30, 60 and 240 mg for 3 days. The selection of these dose levels are based on the doses being used in the ongoing Phase 2a studies (IR 60 mg BID) and the safety and PK data from the GSK2982772 FTIH study, where doses up to IR 120 mg BID for 14 days were administered.

In Part A, a single dose of 120 mg MR has been selected since this dose is anticipated to provide systemic exposure similar to the 60 mg BID regimen being used in the ongoing Phase 2a studies (assuming a relative bioavailability of 100%). In the GSK2982772 FTIH study, 120 mg of the IR formulation was well tolerated when administered as single and repeated doses (BID for 14 days). A single 120 mg dose of the MR formulation in a capsule is expected to result in lower C_{max} than for the 120 mg IR tablet, and overall systemic exposure (AUC) is expected to be similar or lower than a single 120 mg IR tablet dose.

The administration of 120 mg MR with food is expected to maintain AUC and C_{max} values within the range of values observed following 120 mg dose in the FTIH study. In the worst case scenario of dose dumping with food, 120 mg MR would have a PK profile similar to a single dose of 120 mg IR.

In Part B, the target daily MR doses of 30, 60, 240 mg reflect the approximate dose range that is planned to be taken forward into the Phase 2b DR studies. The actual dose level may be increased (by adding additional minitabs to the capsule or by giving multiple capsules) if the relative bioavailability of the selected MR at 120 mg is less than 100% compared to a 120 mg dose of the IR tablet. Taking into account the bioavailability of MR relative to IR, it is planned that the highest dose of MR to be administered will be not exceed a total daily dose equivalent to 240 mg IR (e.g. if the bioavailability of MR is 50% that of IR, the maximum daily dose of MR to be administered would be 480 mg).

6. STUDY POPULATION

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

Quotient Clinical 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 Clinical 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:

   A male participant must agree to use a highly effective contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

(ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 30 days before and 30 days after the last dose of study treatment.

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. Part A only: Any history of suicidal behaviour within the past 6 months or any history of attempted suicide in a participant's lifetime.
3. Part B only: Participants with current history of Suicidal Ideation Behaviour as measured using the C-SSRS or a history of attempted suicide.
4. History of clinically significant psychiatric disorders as judged by the investigator. Depression requiring treatment in the last 2 years.
5. History of herpes zoster (shingles) reactivation.
6. History or diagnosis of obstructive sleep apnoea.
7. History of a significant respiratory disorder. Childhood asthma that has fully resolved is permitted.
8. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
9. 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.
10. History of GI surgery (with exception of appendectomy).
11. History of cholecystectomy or gall stones.
12. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active.
13. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
14. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35% of total).

15. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
16. Corrected QT interval (QTc) >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

17. 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).
18. 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

19. 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.
20. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
21. 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.
22. 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

23. Current or history of renal disease or estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation calculation <60 mL/min/1.73m^2 at screening.
24. 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.

25. An elevated C-reactive protein (CRP) outside the normal reference range.
26. Part B only: A positive anti-nuclear antibody (ANA) outside the normal reference range.
27. Confirmed positive pre-study drug/alcohol screen.
28. Positive human immunodeficiency virus (HIV) antibody test.
29. Regular use of known drugs of abuse, or history of drug or alcohol abuse in the past 5 years.

Other Exclusions

30. 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, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
31. 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).
32. 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.
33. Unwilling or unable to swallow multiple size 0-00 capsules as part of study participation.
34. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
35. Total cholesterol ≥300 mg/dL (≥7.77 millimole [mmol]/Liter [L]) or triglycerides ≥250 mg/dL (≥2.82 mmol/L).
36. Participants who are study site employees, or immediate family members of a study site or sponsor employee.

6.3. Lifestyle Restrictions

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.

  If BID dosing in the fasted state is selected for Part B, participants will be dosed in the evening approximately 12 hours after the morning dose. Meals will be provide as described above (i.e., no food will be permitted 2 hours before and 2 hours after dosing).
- For dosing after a high fat breakfast (Part A) or a standard breakfast (Part B), participants will be provided with a light snack 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 min, with dosing occurring 30 min after the start of breakfast. Participants should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 min after the start of breakfast. 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.

  If BID dosing administered with food is selected for Part B, participants will be dosed in the evening following a standard evening meal. Meals will be provided as described above (with evening dosing approximately 30 minutes after the start of the evening meal).
- If drug administration in Part B is in the fasted stated, then on Day 2 when PK samples are not being collected, meals will be provided at appropriate times, i.e., a standard breakfast at approximately 2 hours post-morning dose, lunch at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post-morning dose.
- If drug administration in Part B is in the fed state, then on Day 2 when PK samples are not being collected, meals will be provided at appropriate times, i.e., a standard breakfast 30 mins prior to the morning dose, lunch at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post-morning dose.
- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, 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 (eg, 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 (Optional)	F (Optional)
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	Prototype MR Minitablet in Capsule Formulation A	Prototype MR Minitablet in Capsule Formulation B	IR Tablet Reference	Prototype MR Minitablet in Capsule Formulation A, B or C	Prototype MR Minitablet in Capsule Formulation A, B, C or D	Prototype MR Minitablet in Capsule Formulation A, B, C or D
Unit dose strength(s)/ Dosage level(s):	60 mg / 120 mg	60 mg / 120 mg	30 mg / 120 mg	60 mg / 120 mg	60 mg / 120 mg	60 mg / 120 mg
Route of Administration	Oral with 240 mL water					
Dosing instructions:	2 capsules, on the morning of Day 1 following an overnight fast	2 capsules, on the morning of Day 1 following an overnight fast	4 tablets in the morning of Day 1 following an overnight fast	2 capsules, on the morning of Day 1 following an overnight fast (if Formulation C) or following a high fat breakfast (if Formulation A or B)	2 capsules, on the morning of Day 1 following an overnight fast (if Formulation D) or following a high fat breakfast (if Formulation A, B or C)	2 capsules, on the morning of Day 1 following a high fat breakfast

Regimen	**A**	**B**	**C**	**D**	**E (Optional)**	**F (Optional)**
Packaging and Labelling	Study Treatment will be provided in 60 mL Duma bottle. Each Duma bottle will be labelled as required per country requirement.					
Manufacturer	Quotient	Quotient	Quotient	Quotient	Quotient	Quotient

7.1.2. Treatments Administered - Part B

Regimen	G	H	I
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	Prototype MR Minitablet in Capsule Formulation X	Prototype MR Minitablet in Capsule Formulation X	Prototype MR Minitablet in Capsule Formulation X
Unit dose strength(s)/ Daily Dosage level(s)[a]:	15 or 30 mg / 30 mg	30 or 60 mg / 60 mg	60 mg / 240 mg
Route of Administration	Oral with 240 mL water		
Dosing instructions:	1 x 30 mg capsule in the morning of Days 1 to 3 or 1 x 15 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)	1 x 60 mg capsule in the morning of Days 1 to 3 or 1 x 30 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)	4 x 60 mg capsule in the morning of Days 1 to 3 or 2 x 60 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)
Packaging and Labelling	Study Treatment will be provided in 60 mL Duma bottle. Each Duma bottle will be labelled as required per country requirement.		
Manufacturer	Quotient		

Formulation X is the formulation selected from Part A

[a] Daily dosage levels are the anticipated dose levels for Part B; but may be subject to change depending on the results from Part A.

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 a minimum of 12 participants in Part A, and the maximum daily dose will not exceed a total daily dose equivalent to 240 mg IR 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 480 mg).

The decision to proceed to the next dose level of GSK2982772 (either an increase or a decrease) 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 5.1.1.

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 Subject 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 authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized 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 (ie, 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 workbook and electronic Case Report Form (eCRF) 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

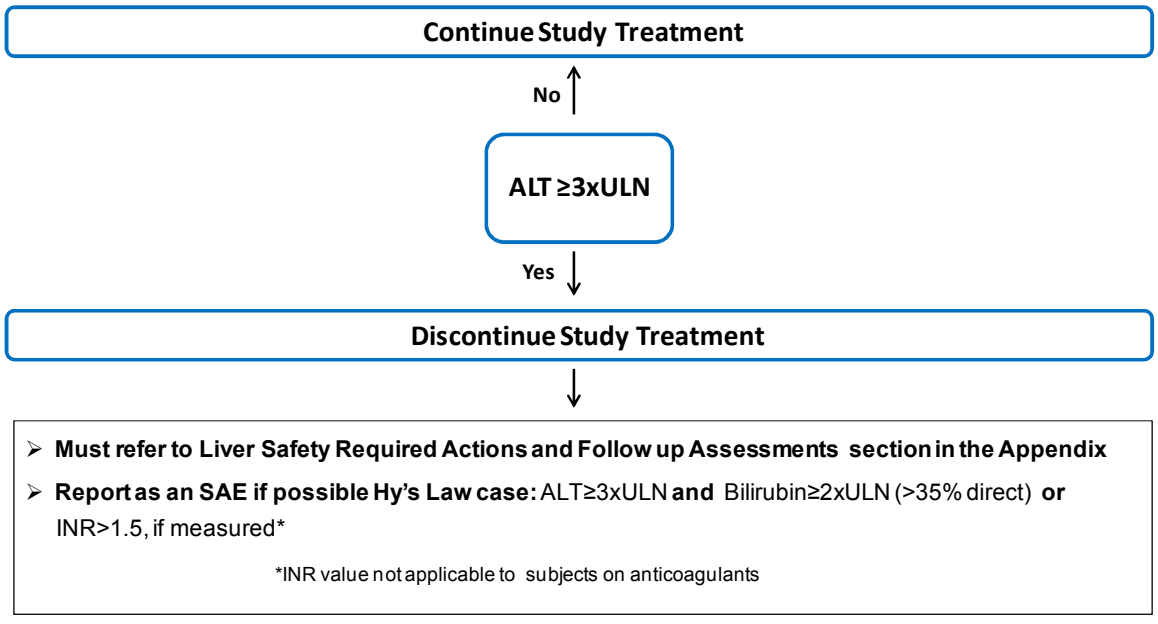
See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

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 6.

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 (e.g., 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 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, after consultation with the medical monitor, 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.

8.1.5. Rechallenge

8.1.5.1. Study Treatment Restart or Rechallenge

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

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 Case Report Form (CRF).
- 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 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 workbook.
- 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:

- The occurrence of an SAE, considered at least possibly related to the IMP administration in one participant.
- The occurrence of severe non-serious AEs considered as, at least, possibly related to the IMP administration in 2 participants at the same dose level

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 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 halted, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable, should 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 temporary suspension 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 may 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 summarized in the SoA.
- 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, 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 (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- 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 56-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 32 hours post-dose (Part A, Treatment Periods 1, 2, 4, 5, 6) or 24 hours post-dose (Part A, Treatment Period 3) or 24 hours after the last dose (Part B Treatment Periods 1, 2 and 3; if BID dosing selected this will be after the last evening dose) 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 CRF 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, stabilized, 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 eg, 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 30 days after the last dose.
- 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 (eg, spontaneous abortion, fetal 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 CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

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 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 (e.g. 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 (e.g. 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 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:
  - The pre-dose blood sample will be taken ≤2 hours before dosing
  - 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:
  - The pre-dose urine sample will be taken ≤3 hours before dosing or the first void of the day
  - 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 CRF. The laboratory reports must be filed with the source

documents. Clinically significant abnormal laboratory findings are those which 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.
- 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 CRF.

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.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening C-SSRS' will be completed in Part B only. Assessments done at Day 4, the 'Since Last Visit C-SSRS' will be completed in Part B only. GSK Version 4.1 of both rating scales will be used.

Participant s who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their General Practitioner or appropriate psychiatric care and be discontinued from study medication. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 9.2). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in

the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

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

Genetics are not evaluated in this study.

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}, $AUC_{(0-inf)}$, C_{12} and C_{24} and peak to trough concentration ratio for each test minitab MR formulation in a capsule (120 mg) relative to the IR formulation (120 mg).

10.2. Sample Size Determination

10.2.1. Sample Size Determination - Part A

To date, there are no MR formulation variability data available. The maximum between-subject coefficient of variation (CV_b) for the PK parameters observed in Study 200975 following GSK2982772 capsule formulation were used for precision estimates; CV_b (%) for $AUC_{(0-inf)}$ and C_{max} for 120 mg GSK2982772 IR capsule formulation were 29.0 and 31.5 respectively. Therefore, the estimates of within subject coefficient of variation (CV_w [%]) are 20.3% and 18.8% for $AUC_{(0-inf)}$ and C_{max}, respectively. 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 15.3% and 14.2% of the point estimate respectively.

Since it is expected that the MR formulation is to reduce the C_{max} by 50% whilst maintaining the AUC, a sample size of 12 ensures that the 90% CI is within the region 0.8-1.25 for AUC and 0.4-0.625 for C_{max}, if the observed geometric ratio is 0.93-1.08 for AUC and 0.47-0.54 for C_{max}.

Sample Size Sensitivity – Part A

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability observed in Study 200975, the precision of these estimates calculated as half width of a 90% confidence interval for the mean ratio (MR/IR) and expressed as distance from mean to limits for 10, 12, 14 and 16 participants has been calculated (Table 5).

Table 5 Precision Estimate of Mean – Part A

CVw (%)	Precision of Mean (%)			
	N=10	N=12	N=14	N=16
15	12.70	11.30	10.30	9.50
18.8	16.00	14.20	12.90	11.90
20	17.30	15.30	13.90	12.90

For example, based upon the estimate of variability (CV_w%) of 20 and a sample size of 14, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 13.9% of the point estimate.

10.2.2. Sample Size Determination - Part B

No repeat dose MR formulation variability data are currently available. Therefore, the maximum CV_b for the PK parameters were observed in the study 200972 following repeat dose of GSK2982772 capsule formulation; CV_b (%) for $AUC_{(0-\tau)}$ and C_{max} for 20mg QD GSK2982772 IR capsule formulation on Day 1 is 36.1 and 27.1 respectively. Therefore, the estimates of equivalent CV_w (%) are 23.2 and 17.6 for C_{max} and $AUC_{(0-\tau)}$ respectively. Based on these estimates of variability and a sample size of 8 completers, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of $AUC_{(0-\tau)}$ and C_{max} will be within approximately 12.1% and 16.7% of the point estimate respectively.

Sample Size Sensitivity – Part B

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability, the precision of these estimates calculated as half width of a 90% confidence interval for the mean and expressed as distance from mean to limits for 4, 6, 8 and 10 participants has been calculated (Table 6).

Table 6 Precision Estimate of Mean – Part B

CV_b (%)	Precision of Mean (%)			
	N=4	N=6	N=8	N=10
18.4%	23.6	16.0	12.8	11.0
19.3%	25.1	16.9	13.6	11.6
24.4%	32.6	21.8	17.4	14.9
25.5%	34.2	22.8	18.2	15.6

For example, based upon the estimate of variability (CV_b%) of 19.3 and a sample size of 4, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 25.1% 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.

In Part A, from 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 12 hours and 24 hours post-dose (C_{12h} and C_{24h}).
- area under the plasma concentration vs time curve (AUC(0-t), AUC(0-24), AUC(0-12) and AUC(0-inf)).
- the percentage of AUC extrapolated beyond the last measured time point (AUC%extrap).
- terminal half-life (t1/2).
- C_{max} to C_{12h} and C_{max} to C_{24h} ratios.

- relative bioavailability ($Frel_{formulation}$) of test formulations 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 vs fasted based on AUC and $C_{max.}$

In Part B, from the plasma concentration-time data for each of the regimens, the following PK parameters will be determined, for Day 1 and Day 3, as data permit:

- maximum observed plasma concentration (C_{max}) for QD dosing. If BID dosing, C_{max} after morning dose and evening dose.
- time to C_{max} (T_{max}) for QD dosing. If BID dosing, T_{max} after morning dose and evening dose.
- observed concentration at 12 hours and 24 hours post-dose (C_{12h} and C_{24h}).
- area under the plasma concentration-time curve ($AUC_{(0-24)}$) for QD dosing. If BID dosing, $AUC_{(0-12)}$ and $AUC_{(12-24).}$
- C_{max} to C_{12} and C_{max} to C_{24} ratios.
- Dose normalised C_{max}, C_{12h}, C_{24h}, $AUC_{(0-tau)}$ (for BID dosing), $AUC_{(0-24)}$ and $AUC_{\mathbf{(0-inf).}}$

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 loge-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. Ratio of $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}24)}$, ($AUC_{(0\text{-}t)}$, if $AUC_{(0\text{-}inf)}$ cannot be derived), C_{max}, C_{12} and C_{24} for MR formulation to IR formulation will be computed with 90% CI. C_{max} to C_{12h} and C_{max} to C_{24h} ratio for each minitab MR formulation (120 mg) and the IR formulation (120 mg) will be computed with 90% CI.
Secondary	The secondary endpoints for food effect will be summarised descriptively. In addition, log-transformed $AUC_{(0\text{-}inf)}$ ($AUC_{(0\text{-}t)}$, if $AUC_{(0\text{-}inf)}$ cannot be derived), C_{12h}, 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 be computed for the differences in GSK2982772 MR formulation (120 mg) 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 of GSK2982772 (120 mg) 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 formulation at target daily doses of 30, 60 and 240 mg will be summarised descriptively. Plots of dose vs dose normalised $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$ ($AUC_{(12\text{-}24)}$ BID dosing), C_{12h}, C_{24h} and C_{max} (after morning and evening doses if BID dosing) will be generated to determine if there are any dose dependent changes in the absorption of GSK2982772 following repeat dose administration of the selected minitab MR formulation.

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 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 of preceding periods. There will be the option to either optimise the MR release duration and/or to evaluate the impact of food on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 2.

There will be an interim review following final period of Part A to determine the formulation, doses, dosing frequency (QD or BID) and prandial state for Part B. The data will be sent to the sponsor by Quotient, from which the decision on formulation 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, CPMS and GCSP). The decision will be documented and signed by the PI as per Quotient Clinical current SOP. Evidence of the decision will be retained in the ISF and GSK Trial Master File.

There will be no interim analysis during Part B of the study.

See Section 5.1.1 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, 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 or if the PK profiles indicate that a QD or BID dosing regimen isn't feasible. 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.

- Administration of MR with a high-fat meal shows dose dumping

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
AST	Aspartate Aminotransferase
AUC	Area under the concentration vs time curve
$AUC_{(0-12)}$,	Area under the curve from time zero to 12 hours
$AUC_{(0-24)}$	Area under the curve from time zero to 24 hours
$AUC_{(0-t)}$	Area under the curve from time zero to the last measurable concentration
BID	Twice daily
BUN	Blood Urea Nitrogen
C_{12}	Concentration at 12 h post-dose
C_{24}	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
CPMS	Clinical Pharmacokinetics Modelling and Simulation
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CV_b	Between subject coefficient of variation
CV_w	Within subject coefficient of variation
DR	Dose ranging
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FTIH	First time in human
Frel	Relative bioavailability
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice

HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human Chorioninc Gonadotropin
HIV	Human immunodeficiency virus
HIPPA	Health Insurance Portability and Accountability Act
HRT	Hormonal Replacement Therapy
ICF	Informed consent form
IEC	Independent Ethics Committees
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Immediate release
IRB	Institutional Review Board
ISF	Investigator site file
IVIVT	In Vitro/In Vivo Translation
L	Litre
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
mg	milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
mins	Minutes
mL	Millilitres
mmol	Millimole
MR	Modified release
MSDS	Material Safety Data Sheet
msec	Milliseconds
NOAEL	No observed adverse effect level
Pgp	P-glycoprotein
PI	Principal investigator
PIS	Participant Information Sheet
PK	Pharmacokinetic(s)
ppm	Parts per million
PsO	Plaque psoriasis
PSRAE	Possible Suicidality Related Adverse Event
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
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}
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
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Chiron RIBA
SAS
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 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 7 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	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • 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], and hepatitis C virus antibody) at screening only • Tuberculosis test (QuantiFERON) at screening only • C-reactive protein (CRP) at screening only • Anti-nuclear antibody (ANA) in Part B only The results of each test must be entered into the CRF.

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 6 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 Governance 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 workbook 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 workbook 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 authorized 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 authorized 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 CRF 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 CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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 source data verification to confirm that data entered into the CRF by authorized 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 reported on the CRF or entered in the eCRF 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 last visit of the last participant (eg follow-up assessment). 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 jeopardize 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 CRF (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 CRF page. • 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 utilized 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 recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within 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 eCRF (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 eCRF. • 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)

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

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-hormonal 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.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- Refrain from donating sperm for duration of study and for 3 months after study completion or from last dose.
- As there is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male participants, a condom should be used by all male participants during the protocol-defined time frame in Section 6.1.

Female participants

Female participants who are not of childbearing potential do not need to use any methods of contraception.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *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
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If*

not, an additional highly effective method of contraception should be used.)
Sexual abstinence (*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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing will be performed at admission to each study period and at the follow-up visit
- 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 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 CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

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 Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize 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 CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. 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 CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

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

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.

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

Urgent Safety Measures

If Quotient Clinical 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 Clinical may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

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

Reporting of Urgent Safety Issues

Quotient Clinical 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: Protocol Amendment History

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

TITLE PAGE

Protocol Title: A two part, non-randomised, open label study designed to assess the pharmacokinetics of GSK2982772 following administration of modified release formulations in capsule relative to an immediate release reference tablet formulation (Part A) and the pharmacokinetics of escalating, repeat doses of a selected modified release prototype (Part B) in healthy subjects

Protocol Number: 205017

Short Title: A study to compare the pharmacokinetics of GSK2982772 following administration of different modified release formulations in capsule relative to an immediate release tablet formulation and to investigate the pharmacokinetics of a selected modified release formulation in capsule following repeat doses for 3 days.

Compound Number: GSK2982772

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 2017-000652-25

Approval Date: 07-JUL-2017

SPONSOR SIGNATORY:

PPD

July 7th 2017

Ramiro Castro-Santamaria
Vice President & Head Unit Physician
Immunoinflammation Therapy Area

Date

PPD

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1. SYNOPSIS

Protocol Title: A two part, non-randomised, open label study designed to assess the pharmacokinetics of GSK2982772 following administration of modified release formulations in capsule relative to an immediate release reference tablet formulation (Part A) and the pharmacokinetics of escalating, repeat doses of a selected modified release prototype (Part B) in healthy subjects.

Short Title: A study to compare the pharmacokinetics of GSK2982772 following administration of different modified release formulations in capsule relative to an immediate release tablet formulation and to investigate the pharmacokinetics of a selected modified release formulation in capsule following repeat doses for 3 days.

Rationale: The purpose of this study is to evaluate a modified release (MR) formulation of GSK2982772 using a minitab approach filled into a capsule in order to develop a more convenient once daily (QD) dosing formulation. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. Initially, the pharmacokinetic (PK) profiles of slow (approximately 24 hours) and fast (approximately 10 hours) release rates of MR minitab will be compared to the PK profile of the immediate release (IR) tablet. In subsequent arms of the study, the release rate may be adapted to achieve the target PK profile. The effect of a high fat meal on the absorption of GSK2982772 when co-administered with the selected minitab MR formulation will be evaluated to ensure that dose dumping does not occur. In addition, the PK profile of repeat doses at 3 dose levels will be evaluated to ensure that the MR formulation can achieve a sufficient GSK2982772 systemic exposure range to support the Phase IIb dose ranging (DR) studies.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each test MR formulation in a capsule (120 mg) compared to the IR formulation (120 mg)	• 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 $AUC_{(0\text{-}24)}$, area under the curve from time zero to 12 hours $AUC_{(0\text{-}12)}$, maximum observed concentration (C_{max}), Concentration at 12 hours post-dose (C_{12h}), Concentration at 24 hours post-dose (C_{24h}) and ratio of C_{max} : C_{1h2} and C_{max} : $C_{24h,}$ relative bioavailability ($FreI_{formulation}$) based on AUC and C_{max}
Secondary	
• To assess the impact of high fat meal on the PK of GSK2982772 following single dose administration of the selected MR formulation in a capsule (120 mg)	• GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t),}$ C_{max} and time to C_{max} (T_{max}), $FreI_{FE}$ based on AUC and C_{max}
• To determine if there are any dose dependant changes in the absorption of GSK2982772 following repeat dose administration of the selected MR formulation in a capsule at target daily doses of 30, 60 and 240 mg	• GSK2982772 $AUC_{(0\text{-}24)}$, C_{max} and T_{max} if once daily (QD) dosing, on Day 1 and Day 3 • GSK2982772 $AUC_{(0\text{-}12)}$, $AUC_{(12\text{-}24),}$, C_{max} and T_{max} after morning dose, C_{max} and T_{max} after evening dose if twice daily (BID) dosing, on Day 1 and Day 3
• To assess the safety and tolerability of single doses of GSK2982772 IR formulation and single and repeat doses of the MR formulation in a capsule	• 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

Overall Design:

This is an open label, single centre, two part, single and repeat dose study in healthy male and female participants to assess MR minitab formulations of GSK2982772 in a capsule. Assuming a suitable MR minitab formulation in a capsule is identified, the impact of food (high-fat meal) on the rate and extent of absorption will be evaluated as well as an assessment of the relationship between dose and systemic exposure to GSK2982772 following repeat dosing for 3 days.

Part A of the study is a non-randomised 6 period, sequential, 6-way fixed sequence design in which up to 4 MR minitab formulations in a capsule may be evaluated following single dose administration in the fasted state (120 mg). Periods 1, 2 and 3 will evaluate a slow MR release duration (nominally 24 hours), a fast MR release duration (nominally 10 hours), and IR tablet, 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/or to evaluate the impact of food (high-fat meal) on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 2.

Part B of the study will be an open-label, repeat dose study in which the selected MR minitab formulation in a capsule will be evaluated following 3 days repeat dosing of GSK2982772 at target daily doses of 30, 60 and 240 mg. In Part B, administration of the MR minitab formulation in a capsule will either be in the fasted state or with a standard meal (non-high fat), depending on the results of the food effect assessment in Part A. The frequency of dosing in Part B will either be QD or BID depending on the PK profile in Part A. Whether dosing is QD or BID, the total daily doses will remain the same.

Number of Participants:

Sixteen participants will be enrolled into Part A of the study to allow for the completion of at least 12 evaluable participants. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen). 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.

Ten participants will be enrolled into Part B of the study to allow for the completion of at least 6 evaluable participants. An evaluable participant will have received all 3 doses and completed the planned safety and PK assessments up to 24 hours after the last dose.

Treatment Groups and Duration:

In Part A, each participant will be enrolled in the study for approximately 8 to 13 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 will consist of 3 days and 2 nights followed by a minimum washout of 7 days between doses.

A follow-up visit will occur at least 7 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 9 weeks. Participation will include a screening evaluation within 28 days of study treatment administration and 3 separate 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 will consist of a 5 day, 4-night inpatient period with a minimum of 7 days washout between the last morning dose of one period and the first dose of the next period. A follow-up visit will occur at least 7 days after the last study treatment.

2. SCHEDULE OF ACTIVITIES (SOA)

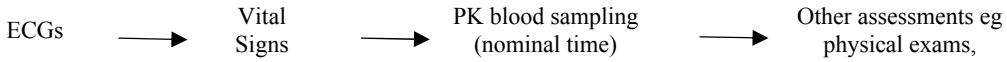
The schedules of activities for Part A and Part B are presented in Table 1 and Table 3, respectively. The time points for the PK blood sample collection in Part A and Part B are presented in Table 2 and Table 4, respectively.

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 must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The 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 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:



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 Part A

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2		
Informed consent	X					
Inclusion and exclusion criteria[1]	X					1. Recheck clinical status before 1st dose of study medication.
Demography	X					
Demonstrate ability to swallow size 0-00 capsules	X					
Full physical examination including height and weight	X					
Brief physical examination		X		X[2]	X	2. Discharge (32 h post-dose for Treatment Period 1, 2, 4, 5 and 6 24 h post-dose for Treatment Period 3)
Medical history (includes substance usage)[3]	X					3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X					
FSH (as needed in women of non-childbearing potential only)	X					
Serum pregnancy test (WOCBP only)	X				X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3, 4, 5, 6 Day			Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2		
Urine pregnancy test (WOCBP only)		X				
Human Immunodefeciency Virus (HIV),, Hepatitis B and C screening[4]	X					4. 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	X[5]	X[5]	X	5. Pre-dose (Treatment Period 1 only) and 24 h post-dose Allowable windows in Section 9.4.4
Glomerular filtration rate	X					
C-reative protein (CRP)	X					
12-lead ECG	X[6]	X	X7	X8	X	6. In triplicate 7. Pre-dose and 2 and 12 h post-dose 8. 24 h post-dose Allowable windows in Section 9.4.3

Procedure	**Screening (up to 28 days before Day 1)**	**Treatment Period 1, 2, 3, 4, 5, 6 Day**			**Follow-up/Study Discontinuation (7 days post last dose)**	**Notes**
		–1	**1**	**2**		
Vital signs	X	X	X[9]	X[10]	X	9. Pre-dose and 2 and 12 h post-dose 10. 24 h post-dose Allowable windows in Section 9.4.2
Study treatment			X			
AE review		←==========		==========→	X	
Serious AE (SAE) review	X	←==========		==========→	X	
Concomitant medication review		←==========		==========→	X	
PK blood sample collection			X[11]	X[11]		11. Time points in Table 2

Table 2 Pharmacokinetic Blood Sample Collection Times – Part A

	Treatment Periods 1, 2, 4, 5 and 6 (MR Formulations)																	
Time (h)	**Pre-dose**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**
Dosing		X																
PK sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

Table 3 Schedule of Activities for Part B

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
Informed consent	X							
Inclusion and exclusion criteria[1]	X							1. Recheck clinical status before 1st dose of study medication.
Demography	X							
Demonstrate ability to swallow size 0-00 capsules	X							
Full physical examination including height and weight	X							
Brief physical examination		X				X[2]	X	2. Discharge (24 h after the last dose)
Medical history (includes substance usage)[3]	X							3. Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X							
FSH (as needed in women of non-childbearing potential only)	X							
Serum pregnancy test (WOCBP only)	X						X	
Urine pregnancy test (WOCBP only)		X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
HIV, Hepatitis B and C screening[4]	X							4. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Tuberculosis 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	X[5]			X[6]	X	5. Pre-dose 6. 24 h after the last dose Allowable windows in Section 9.4.4
Glomerular filtration rate	X							
CRP	X							
ANA	X					X[7]		7. 24 h after the last dose

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
12-lead ECG	X[8]	X	X[9]	X[10]	X[9]	X[11]	X	8. In triplicate 9. Pre-dose and 2 and 12 h post-dose 10. Pre-dose 11. 24 h after the last dose Allowable windows in Section 9.4.3 Time points may be subject to change depending on results from Part A
Vital signs	X	X	X[12]	X[13]	X[12]	X[14]	X	12. Pre-dose and 2 and 12 h post-dose 13. Pre-dose 14. 24 h after the last dose Allowable windows in Section 9.4.2 Time points may be subject to change depending on results from Part A
Columbia Suicide Risk questionnaire	X		X[15]			X[16]		15. Pre-dose 16. 24 h after last dose of each period
Study treatment			X	X	X			
AE review		←==========				==========→	X	
SAE review	X	←==========				==========→	X	
Concomitant medication review		←==========				==========→	X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period 1, 2, 3 Day					Follow-up/Study Discontinuation (7 days post last dose)	Notes
		–1	1	2	3	4		
PK blood sample collection			X[17]	X[17]	X[17]	X[17]		17. Time points in Table 4

Table 4 Pharmacokinetic Blood Sample Collection Times – Part B

	Periods 1, 2 and 3													
	Days 1 and 3													
Time (h)	**Pre-dose**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Dosing[a]		X												
PK sampling[b]	X		X	X	X	X	X	X	X	X	X	X	X	X[c]

[a] Subjects will be dosed on Days 1, 2 and 3; however, no PK samples will be taken post-dose on Day 2

[b] PK sampling schedule may be amended based upon the PK data from Part A and/or if BID dosing is selected for Part B. If BID dosing is employed the number of PK samples may be reduced i.e. some of the samples between 14 and 24 h may not be required. In addition, the 12 h sample will be taken prior to administering the second daily dose.

[c] Day 1 24 h post-dose sample should be taken prior to dosing on Day 2.

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. Study Rationale

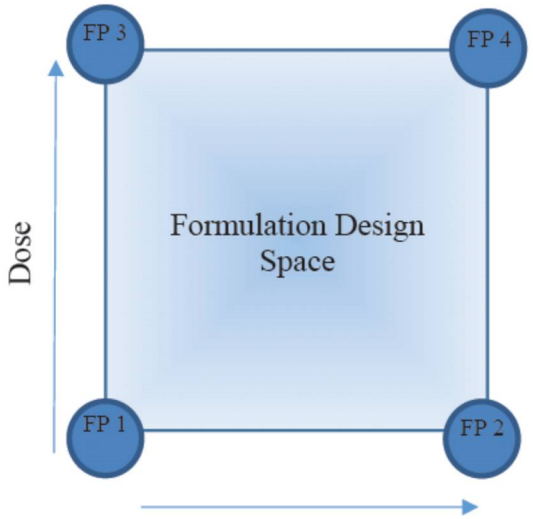
Pharmacokinetic data from the first time in human (FTIH) study for GSK2982772 (200975) [GlaxoSmithKline Document Number 2014N204126_02] showed that the half-life of GSK2982772 was short (~2 to 3 hours). As a result, BID and three times daily (TID) dosing regimens are being evaluated in three ongoing proof of mechanism studies. A QD formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. This current study is being conducted to evaluate the feasibility of developing an MR formulation using a minitab approach filled into a capsule. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. In addition, the number of minitabs included in the capsule can be varied to adjust the dose.

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 Clinical (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.

There will be the option to test a range of formulations based on a 2-dimensional design space describing the dose level and release rate of the IMP (Figure 1).

Figure 1 Two-Dimensional Design Space for the Modified Release Formulation



3.2. 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_02].

3.3. Benefit/Risk Assessment

To date, approximately 124 participants have been enrolled in 4 clinical studies with GSK2982772. In Study 200975, GSK2982772 was administered up to 120 mg BID for 14 days. A total of 67 participants received GSK2982772 and 26 participants received placebo (including crossover) in that study. In the ongoing Phase 2a studies in PsO Study (203167), RA (Study 203168) and Ulcerative Colitis (Study 202152), a total of approximately 26 participants have been randomised to GSK2982772 60 mg BID. Overall, GSK2982772 has been generally well tolerated and no drug-related SAEs have been reported. In Study 203167, there was a death of a 19-year-old male participant due to an accidental overdose with 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 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).

Limited reproductive toxicity studies have been conducted with GSK2982772 to date. 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 30 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. **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_02]. No drug-associated CNS AEs were identified and no SAEs were reported.	**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.
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids.	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, HIV, Hepatitis B and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: In the FTiH study, no SAEs were reported. One subject experienced an Adverse Effect (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded Investigator determined this to be potentially drug-related.	C, and excluded from the study if positive. **Subject Monitoring**: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 8.1.3).
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (eg, inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (eg, risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
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 Investigtor's Brochure for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02].	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related AEs. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data: In the FTIH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO_2, oxygen saturation and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related AEs were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based upon pre-clinical studies. **Clinical data**: In the FTIH study, there have been some reports of lethargy, abnormal dreams, and depressed mood. No events of suicidal ideation or behaviour or changes in behaviour were reported.	**Subject Selection**: • Subjects with a current history of suicidal ideation and behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Subjects receiving multiple doses should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel using the C-SSRS in all subjects receiving multiple doses. See Section 9.4.5.
Reproductive toxicity	**Non-clinical data:** In an early rat embryofoetal development study, there was no maternal or developmental toxicity at doses ≤200 mg/kg/day. In a rabbit embryofoetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection**: • Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for 30 days before first administration of study drug until 30 days (females) and 90 days (males) after the last administration of study drug (Appendix 5). • Females of childbearing potential will undergo serum pregnancy test at screening and follow-up and then urine pregnancy testing at regular intervals during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria**: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates, P-glycoprotein (Pgp) inhibitors and OAT3 substrates were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of OAT3 substrates. 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_02].	**Subject Selection:** • No concomitant medications will be permitted in this study with the exception of 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 and the medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, Labs, etc).

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize 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

Objectives	Endpoints
Primary	
• To evaluate the single dose PK profile of GSK2982772 from each test MR formulation in a capsule (120 mg) compared to the IR formulation (120 mg)	• GSK2982772 area under the curve from time zero to infinity ($AUC_{(0-inf)}$), area under the curve from time zero to the last measurable concentration $AUC_{(0-t)}$, area under the curve from time zero to 24 hours $AUC_{(0-24)}$, area under the curve from time zero to 12 hours $AUC_{(0-12)}$, maximum observed concentration (C_{max}), Concentration at 12 hours post-dose (C_{12h}), Concentration at 24 hours post-dose (C_{24h}) and ratio of C_{max} : C_{1h2} and C_{max} : $C_{24h,}$ relative bioavailability ($FreI_{formulation}$) based on AUC and C_{max}
Secondary	
• To assess the impact of high fat meal on the PK of GSK2982772 following single dose administration of the selected MR formulation in a capsule (120 mg)	• GSK2982772 $AUC_{(0-inf)}$, $AUC_{(0-t),}$ C_{max} and time to C_{max} (T_{max}), $FreI_{FE}$ based on AUC and C_{max}
• To determine if there are any dose dependant changes in the absorption of GSK2982772 following repeat dose administration of the selected MR formulation in a capsule at target daily doses of 30, 60 and 240 mg	• GSK2982772 $AUC_{(0-24)}$, C_{max} and T_{max} if once daily (QD) dosing, on Day 1 and Day 3 • GSK2982772 $AUC_{(0-12)}$, $AUC_{(12-24),}$, C_{max} and T_{max} after morning dose, C_{max} and T_{max} after evening dose if twice daily (BID) dosing, on Day 1 and Day 3
• To assess the safety and tolerability of	• Adverse events (AEs)

Objectives	Endpoints
single doses of GSK2982772 IR formulation and single and repeat doses of the MR formulation in a capsule	• 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

5. STUDY DESIGN

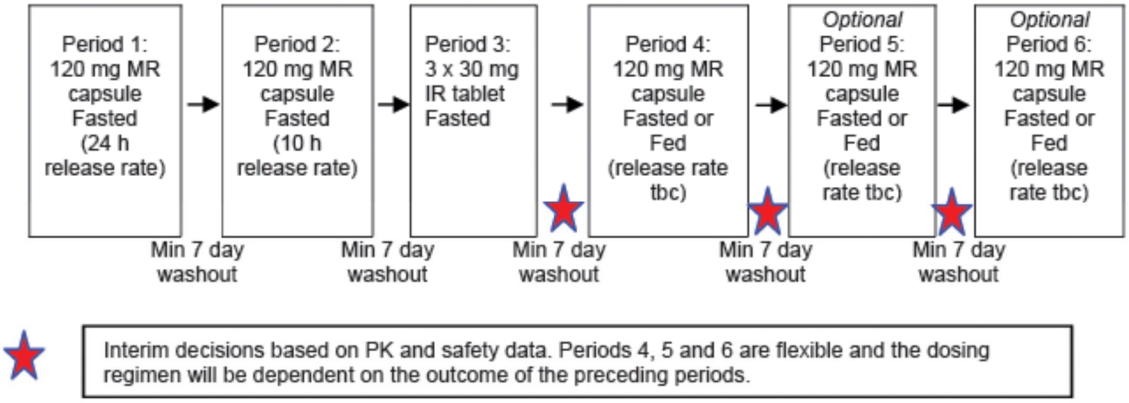
5.1. Overall Design

This is an open label, single centre, two part, single and repeat dose study in healthy male and female participants to assess MR minitab formulations of GSK2982772 in a capsule. Assuming a suitable MR minitab formulation in a capsule is identified, the impact of food (high-fat meal) on the rate and extent of absorption will be evaluated as well as an assessment of the relationship between dose and systemic exposure to GSK2982772 following repeat dosing for 3 days.

Part A of the study is a non-randomised 6 period, sequential, 6-way fixed sequence design in which up to 4 MR minitab formulations in a capsule may be evaluated following single dose administration in the fasted state (120 mg) (Figure 2). Periods 1, 2 and 3 will evaluate a slow MR release duration (nominally 24 hours), a fast MR release duration (nominally 10 hours), and IR tablet, 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/or to evaluate the impact of food (high-fat meal) on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 to 2.

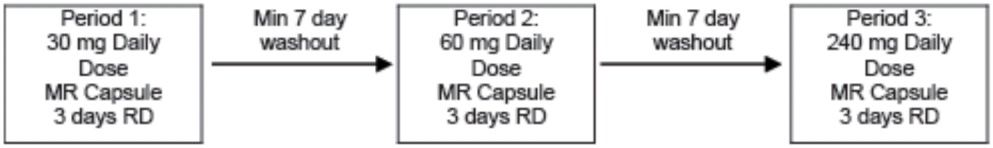
Subjects will be admitted to the clinic in the morning of the day before dosing (i.e. Day -1) of each inpatient period. Each inpatient period will consist of 3 days and 2 nights followed by a minimum washout of 7 days between doses. A follow-up visit will occur at least 7 days after the last study treatment. Participants will receive a single oral dose of study treatment during each inpatient period.

Figure 2 Part A Study Design – Formulation Optimisation and Food Effect



Part B of the study will be an open-label, repeat dose study in which the selected MR minitab formulation in a capsule will be evaluated following 3 days repeat dosing of GSK2982772 at target daily doses of 30, 60 and 240 mg (Figure 3). The target dose may be subject to change based upon evaluation of the emerging data from Part A, e.g. if the bioavailability of 120 mg MR formulation in a capsule is less than the 120 mg IR tablet (reference) formulation. In Part B, administration of the MR minitab formulation in a capsule will either be in the fasted state or with a standard meal (non-high fat), depending on the results of the food effect assessment in Part A. The frequency of dosing in Part B will either be QD or BID depending on the PK profile in Part A. Whether dosing is QD or BID, the total daily doses will remain the same. If BID dosing is selected the final dose will be the evening dose of Day 3. 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 will consist of 5 days and 4 nights. There will be a minimum of 7 days washout between the last morning dose of one period and the first dose of the next period. A follow-up visit will occur at least 7 days after the last study treatment.

Figure 3 Part B Study Design – Dose Ranging



5.1.1. Criteria for Interim Decisions

In Part A there will be an interim review following completion of Periods 1 to 3 to determine the formulation and the prandial state for Period 4. Similarly, there will be an interim review following Periods 4 and 5. Following the final period of Part A, the formulation, doses, dosing frequency (QD or BID) and prandial state for Part B will be determined. However, the highest dosing regimen will be selected to ensure that the maximum daily dose will not exceed the equivalent of an IR dose of 240 mg, 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 480 mg). Interim

decisions will only be made after a complete review of all relevant data collected from the previous dose group. Data must be available from a minimum of 12 participants who have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen [Regimen C]). 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 full data, as described below, are not available for 12 participants, the principal investigator (PI), scientific lead and sponsor will take a decision as to whether the data available are sufficient to support the formulation selection decision. If data in fewer than 16 participants are used in the decision process, additional participants will not be dosed to increase the number of participants in the completed regimen.

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

- AEs, vital signs, ECGs, safety laboratory data and physical examinations.
- Plasma concentrations of GSK2982772.
- PK parameter estimates GSK2982772 $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$, T_{max}, C_{max}, C_{12h}, C_{24h} and ratio of C_{max} : C_{12h} and C_{max} : C_{24h}, Frel based on AUC and C_{max} for test vs reference formulations and fed vs fasted, where relevant.
- Protocol deviations will be reviewed to ensure they have had no significant impact on the above data

The decision on formulation 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 Clinical current standard operating procedure (SOP). Evidence of the decision will be retained in the Investigator Site File (ISF) and GSK Trial Master File.

5.2. Number of Participants

In Part A, 16 healthy participants will be enrolled such that at least 12 evaluable participants complete the study. An evaluable participant will have completed the planned safety and PK assessments up to 32 hours after dosing (or 24 hours after dosing for Period 3; IR regimen [Regimen C]). 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.

In Part B, 10 healthy participants will be enrolled such that at least 6 evaluable participants complete the study. An evaluable participant will have received all 3 days of dosing at 2 or more dose levels and completed the planned PK assessments up to 24 hours after the first dose on day 3.

Participants withdrawn due to an IMP-related AE 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 8 replacement participants may be enrolled in Part A. The maximum number of participants that may be dosed in Part A is 24.

Up to 5 replacement participants may be enrolled in Part B. The maximum number of participants that may be dosed in Part B is 15.

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

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 end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

Pharmacokinetic data from the FTIH study for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02] showed that the half-life of GSK2982772 was shorter than predicted (~2 to 3 hours). As a result, BID and TID dosing regimens are being evaluated in three ongoing Phase 2a studies in psoriasis, ulcerative colitis and RA. A QD formulation would be more convenient from a patient perspective and could offer the advantage of providing a flatter GSK2982772 concentration time profile. Therefore, switching to a QD formulation for the Phase 2b DR studies and subsequent Phase 3 studies would be advantageous.

This current study is being conducted to evaluate the feasibility of developing an MR formulation using a minitab approach filled into a capsule. Each minitab will contain 5 mg GSK2982772 and the amount of polymer can be adjusted to achieve the desired in-vitro release profile. The total weight of the minitab will be 20 mg and between 3 and 12 minitabs can be loaded into a capsule for oral administration. Initially the PK profiles of slow (approximately 24 hours) and fast (approximately 10 hours) release rates of MR minitab will be compared to the PK profile of the IR tablet. In subsequent arms of the study, the release rate may be adapted to achieve the target PK profile. The effect of a high fat meal on the absorption of GSK2982772 when co-administered with the selected

minitab MR formulation in a capsule will be evaluated to ensure that dose dumping does not occur. In addition, a range of repeat doses will be evaluated to ensure that the MR formulation in a capsule can achieve a sufficient GSK2982772 systemic exposure range to support the Phase IIb DR studies.

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 Part A, a single dose of 120 mg will be used for the MR minitab formulations in a capsule and for the IR tablet. In Part B, it is planned to evaluate target daily doses of 30, 60 and 240 mg for 3 days. The selection of these dose levels are based on the doses being used in the ongoing Phase 2a studies (IR 60 mg BID) and the safety and PK data from the GSK2982772 FTIH study, where doses up to IR 120 mg BID for 14 days were administered.

In Part A, a single dose of 120 mg MR has been selected since this dose is anticipated to provide systemic exposure similar to the 60 mg BID regimen being used in the ongoing Phase 2a studies (assuming a relative bioavailability of 100%). In the GSK2982772 FTIH study, 120 mg of the IR formulation was well tolerated when administered as single and repeated doses (BID for 14 days). A single 120 mg dose of the MR formulation in a capsule is expected to result in lower C_{max} than for the 120 mg IR tablet, and overall systemic exposure (AUC) is expected to be similar or lower than a single 120 mg IR tablet dose.

The administration of 120 mg MR with food is expected to maintain AUC and C_{max} values within the range of values observed following 120 mg dose in the FTIH study. In the worst case scenario of dose dumping with food, 120 mg MR would have a PK profile similar to a single dose of 120 mg IR.

In Part B, the target daily MR doses of 30, 60, 240 mg reflect the approximate dose range that is planned to be taken forward into the Phase 2b DR studies. The actual dose level may be increased (by adding additional minitabs to the capsule or by giving multiple capsules) if the relative bioavailability of the selected MR at 120 mg is less than 100% compared to a 120 mg dose of the IR tablet. Taking into account the bioavailability of MR relative to IR, it is planned that the highest dose of MR to be administered will be not exceed a total daily dose equivalent to 240 mg IR (e.g. if the bioavailability of MR is 50% that of IR, the maximum daily dose of MR to be administered would be 480 mg).

6. STUDY POPULATION

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

Quotient Clinical 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 Clinical 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:

   A male participant must agree to use a highly effective contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

(ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 30 days before and 30 days after the last dose of study treatment.

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. Part A only: Any history of suicidal behaviour within the past 6 months or any history of attempted suicide in a participant's lifetime.
3. Part B only: Participants with current history of Suicidal Ideation Behaviour as measured using the C-SSRS or a history of attempted suicide.
4. History of clinically significant psychiatric disorders as judged by the investigator. Depression requiring treatment in the last 2 years.
5. History of herpes zoster (shingles) reactivation.
6. History or diagnosis of obstructive sleep apnoea.
7. History of a significant respiratory disorder. Childhood asthma that has fully resolved is permitted.
8. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
9. 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.
10. History of GI surgery (with exception of appendectomy).
11. History of cholecystectomy or gall stones.
12. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active.
13. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
14. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35% of total).

15. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
16. Corrected QT interval (QTc) >450 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

17. 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).
18. 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

19. 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.
20. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
21. 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.
22. 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

23. Current or history of renal disease or estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation calculation <60 mL/min/1.73m^2 at screening.
24. 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.

25. An elevated C-reactive protein (CRP) outside the normal reference range.
26. Part B only: A positive anti-nuclear antibody (ANA) outside the normal reference range.
27. Confirmed positive pre-study drug/alcohol screen.
28. Positive human immunodeficiency virus (HIV) antibody test.
29. Regular use of known drugs of abuse, or history of drug or alcohol abuse in the past 5 years.

Other Exclusions

30. 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, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
31. 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)..
32. 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.
33. Unwilling or unable to swallow multiple size 0-00 capsules as part of study participation.
34. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
35. Total cholesterol ≥300 mg/dL (≥7.77 millimole [mmol]/Liter [L]) or triglycerides ≥250 mg/dL (≥2.82 mmol/L).
36. Participants who are study site employees, or immediate family members of a study site or sponsor employee.

6.3. Lifestyle Restrictions

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.

  If BID dosing in the fasted state is selected for Part B, participants will be dosed in the evening approximately 12 hours after the morning dose. Meals will be provide as described above (i.e., no food will be permitted 2 hours before and 2 hours after dosing).
- For dosing after a high fat breakfast (Part A) or a standard breakfast (Part B), participants will be provided with a light snack 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 min, with dosing occurring 30 min after the start of breakfast. Participants should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 min after the start of breakfast. 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.

  If BID dosing administered with food is selected for Part B, participants will be dosed in the evening following a standard evening meal. Meals will be provided as described above (with evening dosing approximately 30 minutes after the start of the evening meal).
- If drug administration in Part B is in the fasted stated, then on Day 2 when PK samples are not being collected, meals will be provided at appropriate times, i.e., a standard breakfast at approximately 2 hours post-morning dose, lunch at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post-morning dose.
- If drug administration in Part B is in the fed state, then on Day 2 when PK samples are not being collected, meals will be provided at appropriate times, i.e., a standard breakfast 30 mins prior to the morning dose, lunch at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post-morning dose.
- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, 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 (eg, 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 (Optional)	F (Optional)
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	Prototype MR Minitablet in Capsule Formulation A	Prototype MR Minitablet in Capsule Formulation B	IR Tablet Reference	Prototype MR Minitablet in Capsule Formulation A, B or C	Prototype MR Minitablet in Capsule Formulation A, B, C or D	Prototype MR Minitablet in Capsule Formulation A, B, C or D
Unit dose strength(s)/ Dosage level(s):	60 mg / 120 mg	60 mg / 120 mg	30 mg / 120 mg	60 mg / 120 mg	60 mg / 120 mg	60 mg / 120 mg
Route of Administration	Oral with 240 mL water					
Dosing instructions:	2 capsules, on the morning of Day 1 following an overnight fast	2 capsules, on the morning of Day 1 following an overnight fast	4 tablets in the morning of Day 1 following an overnight fast	2 capsules, on the morning of Day 1 following an overnight fast (if Formulation C) or following a high fat breakfast (if Formulation A or B)	2 capsules, on the morning of Day 1 following an overnight fast (if Formulation D) or following a high fat breakfast (if Formulation A, B or C)	2 capsules, on the morning of Day 1 following a high fat breakfast

Regimen	**A**	**B**	**C**	**D**	**E (Optional)**	**F (Optional)**
Packaging and Labelling	Study Treatment will be provided in 60 mL Duma bottle. Each Duma bottle will be labelled as required per country requirement.					
Manufacturer	Quotient	Quotient	Quotient	Quotient	Quotient	Quotient

7.1.2. Treatments Administered - Part B

Regimen	G	H	I
Study Treatment Name:	GSK2982772	GSK2982772	GSK2982772
Dosage formulation:	Prototype MR Minitablet in Capsule Formulation X	Prototype MR Minitablet in Capsule Formulation X	Prototype MR Minitablet in Capsule Formulation X
Unit dose strength(s)/ Daily Dosage level(s)[a]:	15 or 30 mg / 30 mg	30 or 60 mg / 60 mg	60 mg / 240 mg
Route of Administration	Oral with 240 mL water		
Dosing instructions:	1 x 30 mg capsule in the morning of Days 1 to 3 or 1 x 15 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)	1 x 60 mg capsule in the morning of Days 1 to 3 or 1 x 30 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)	4 x 60 mg capsule in the morning of Days 1 to 3 or 2 x 60 mg capsule in the morning and evening of Days 1 to 3; dosing will be 12 hours apart Fasted or Fed (non-high fat meal)
Packaging and Labelling	Study Treatment will be provided in 60 mL Duma bottle. Each Duma bottle will be labelled as required per country requirement.		
Manufacturer	Quotient		

Formulation X is the formulation selected from Part A

[a] Daily dosage levels are the anticipated dose levels for Part B; but may be subject to change depending on the results from Part A.

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 a minimum of 12 participants in Part A, and the maximum daily dose will not exceed a total daily dose equivalent to 240 mg IR 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 480 mg).

The decision to proceed to the next dose level of GSK2982772 (either an increase or a decrease) 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 5.1.1.

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 Subject 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 authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized 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 (ie, 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 workbook and electronic Case Report Form (eCRF) 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

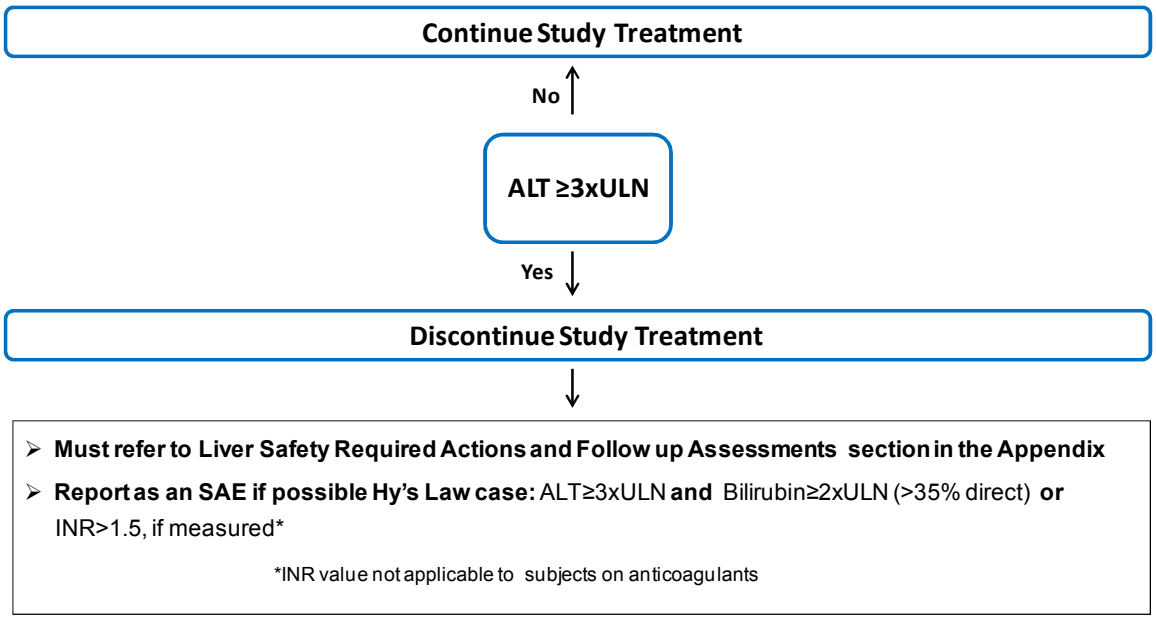
See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

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 6.

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 (e.g., 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 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, after consultation with the medical monitor, 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.

8.1.5. Rechallenge

8.1.5.1. Study Treatment Restart or Rechallenge

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

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 Case Report Form (CRF).
- 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 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 workbook.
- 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:

- The occurrence of an SAE, considered at least possibly related to the IMP administration in one participant.
- The occurrence of severe non-serious AEs considered as, at least, possibly related to the IMP administration in 2 participants at the same dose level

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 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 halted, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable, should 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 temporary suspension 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 may 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 summarized in the SoA.
- 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, 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 (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- 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 56-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 32 hours post-dose (Part A, Treatment Periods 1, 2, 4, 5, 6) or 24 hours post-dose (Part A, Treatment Period 3) or 24 hours after the last dose (Part B Treatment Periods 1, 2 and 3; if BID dosing selected this will be after the last evening dose) 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 CRF 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, stabilized, 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 eg, 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 30 days after the last dose.
- 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 (eg, spontaneous abortion, fetal 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 CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

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 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 (e.g. 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 (e.g. 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 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:
  - The pre-dose blood sample will be taken ≤2 hours before dosing
  - 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:
  - The pre-dose urine sample will be taken ≤3 hours before dosing or the first void of the day
  - 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 CRF. The laboratory reports must be filed with the source

documents. Clinically significant abnormal laboratory findings are those which 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.
- 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 CRF.

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.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening C-SSRS' will be completed in Part B only. Assessments done at Day 4, the 'Since Last Visit C-SSRS' will be completed in Part B only. GSK Version 4.1 of both rating scales will be used.

Participant s who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their General Practitioner or appropriate psychiatric care and be discontinued from study medication. The Medical Monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 9.2). In addition, the Investigator should complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in

the Investigator's opinion, are possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

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

Genetics are not evaluated in this study.

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}, $AUC_{(0-inf)}$, C_{12} and C_{24} and peak to trough concentration ratio for each test minitab MR formulation in a capsule (120 mg) relative to the IR formulation (120 mg).

10.2. Sample Size Determination

10.2.1. Sample Size Determination - Part A

To date, there are no MR formulation variability data available. The maximum between-subject coefficient of variation (CV_b) for the PK parameters observed in Study 200975 following GSK2982772 capsule formulation were used for precision estimates; CV_b (%) for $AUC_{(0-inf)}$ and C_{max} for 120 mg GSK2982772 IR capsule formulation were 29.0 and 31.5 respectively. Therefore, the estimates of within subject coefficient of variation (CV_w [%]) are 20.3% and 18.8% for $AUC_{(0-inf)}$ and C_{max}, respectively. 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 15.3% and 14.2% of the point estimate respectively.

Since it is expected that the MR formulation is to reduce the C_{max} by 50% whilst maintaining the AUC, a sample size of 12 ensures that the 90% CI is within the region 0.8-1.25 for AUC and 0.4-0.625 for C_{max}, if the observed geometric ratio is 0.93-1.08 for AUC and 0.47-0.54 for C_{max}.

Sample Size Sensitivity – Part A

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability observed in Study 200975, the precision of these estimates calculated as half width of a 90% confidence interval for the mean ratio (MR/IR) and expressed as distance from mean to limits for 10, 12, 14 and 16 participants has been calculated (Table 5).

Table 5 Precision Estimate of Mean – Part A

CVw (%)	Precision of Mean (%)			
	N=10	N=12	N=14	N=16
15	12.70	11.30	10.30	9.50
18.8	16.00	14.20	12.90	11.90
20	17.30	15.30	13.90	12.90

For example, based upon the estimate of variability (CV_w%) of 20 and a sample size of 14, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 13.9% of the point estimate.

10.2.2. Sample Size Determination - Part B

No repeat dose MR formulation variability data are currently available. Therefore, the maximum CV_b for the PK parameters were observed in the study 200972 following repeat dose of GSK2982772 capsule formulation; CV_b (%) for $AUC_{(0-\tau)}$ and C_{max} for 20mg QD GSK2982772 IR capsule formulation on Day 1 is 36.1 and 27.1 respectively. Therefore, the estimates of equivalent CV_w (%) are 23.2 and 17.6 for C_{max} and $AUC_{(0-\tau)}$ respectively. Based on these estimates of variability and a sample size of 8 completers, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of $AUC_{(0-\tau)}$ and C_{max} will be within approximately 12.1% and 16.7% of the point estimate respectively.

Sample Size Sensitivity – Part B

Using estimates of parameter (this can be any PK parameter AUC, C_{max}) variability, the precision of these estimates calculated as half width of a 90% confidence interval for the mean and expressed as distance from mean to limits for 4, 6, 8 and 10 participants has been calculated (Table 6).

Table 6 Precision Estimate of Mean – Part B

CV_b (%)	Precision of Mean (%)			
	N=4	N=6	N=8	N=10
18.4%	23.6	16.0	12.8	11.0
19.3%	25.1	16.9	13.6	11.6
24.4%	32.6	21.8	17.4	14.9
25.5%	34.2	22.8	18.2	15.6

For example, based upon the estimate of variability (CV_b%) of 19.3 and a sample size of 4, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of the PK parameter (eg, AUC, C_{max}) will be within approximately 25.1% 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.

In Part A, from 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 12 hours and 24 hours post-dose (C_{12h} and C_{24h}).
- area under the plasma concentration vs time curve (AUC(0-t), AUC(0-24), AUC(0-12) and AUC(0-inf)).
- the percentage of AUC extrapolated beyond the last measured time point (AUC%extrap).
- terminal half-life (t1/2).
- C_{max} to C_{12h} and C_{max} to C_{24h} ratios.
- relative bioavailability ($Frel_{formulation}$) of test formulations 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 vs fasted based on AUC and C_{max}.

In Part B, from the plasma concentration-time data for each of the regimens, the following PK parameters will be determined, for Day 1 and Day 3, as data permit:

- maximum observed plasma concentration (C_{max}) for QD dosing. If BID dosing, C_{max} after morning dose and evening dose.
- time to C_{max} (T_{max}) for QD dosing. If BID dosing, T_{max} after morning dose and evening dose.
- observed concentration at 12 hours and 24 hours post-dose (C_{12h} and C_{24h}).
- area under the plasma concentration-time curve ($AUC_{(0-24)}$) for QD dosing. If BID dosing, $AUC_{(0-12)}$ and $AUC_{(12-24)}$.
- C_{max} to C_{12} and C_{max} to C_{24} ratios.
- Dose normalised C_{max}, C_{12h}, C_{24h}, $AUC_{(0-tau)}$ (for BID dosing), $AUC_{(0-24)}$ and $AUC_{(0-inf)}$.

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 loge-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. Ratio of $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}24)}$, ($AUC_{(0\text{-}t)}$, if $AUC_{(0\text{-}inf)}$ cannot be derived), C_{max}, C_{12} and C_{24} for MR formulation to IR formulation will be computed with 90% CI. C_{max} to C_{12h} and C_{max} to C_{24h} ratio for each minitab MR formulation (120 mg) and the IR formulation (120 mg) will be computed with 90% CI.
Secondary	The secondary endpoints for food effect will be summarised descriptively. In addition, log-transformed $AUC_{(0\text{-}inf)}$ ($AUC_{(0\text{-}t)}$, if $AUC_{(0\text{-}inf)}$ cannot be derived), C_{12h}, 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 be computed for the differences in GSK2982772 MR formulation (120 mg) 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 of GSK2982772 (120 mg) 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 formulation at target daily doses of 30, 60 and 240 mg will be summarised descriptively. Plots of dose vs dose normalised $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}12)}$ ($AUC_{(12\text{-}24)}$ BID dosing), C_{12h}, C_{24h} and C_{max} (after morning and evening doses if BID dosing) will be generated to determine if there are any dose dependent changes in the absorption of GSK2982772 following repeat dose administration of the selected minitab MR formulation.

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 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 of preceding periods. There will be the option to either optimise the MR release duration and/or to evaluate the impact of food on the selected MR minitab formulation in a capsule. There will also be the option to cancel Periods 5 and 6 if an optimal formulation is determined in Periods 1 or 2.

There will be an interim review following final period of Part A to determine the formulation, doses, dosing frequency (QD or BID) and prandial state for Part B. The data will be sent to the sponsor by Quotient, from which the decision on formulation 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, CPMS and GCSP). The decision will be documented and signed by the PI as per Quotient Clinical current SOP. Evidence of the decision will be retained in the ISF and GSK Trial Master File.

There will be no interim analysis during Part B of the study.

See Section 5.1.1 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, 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 or if the PK profiles indicate that a QD or BID dosing regimen isn't feasible. 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.

- Administration of MR with a high-fat meal shows dose dumping

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
AUC	Area under the concentration vs time curve
$AUC_{(0\text{-}12)}$,	Area under the curve from time zero to 12 hours
$AUC_{(0\text{-}24)}$	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_{12}	Concentration at 12 h post-dose
C_{24}	Concentration at 24 h post-dose
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
CPMS	Clinical Pharmacokinetics Modelling and Simulation
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CV_b	Between subject coefficient of variation
CV_w	Within subject coefficient of variation
DR	Dose ranging
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FTIH	First time in human
Frel	Relative bioavailability
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen

hCG	Human Chorioninc Gonadotropin
HIV	Human immunodeficiency virus
HIPPA	Health Insurance Portability and Accountability Act
HRT	Hormonal Replacement Therapy
ICF	Informed consent form
IEC	Independent Ethics Committees
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Immediate release
IRB	Institutional Review Board
ISF	Investigator site file
IVIVT	In Vitro/In Vivo Translation
L	Litre
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
mg	milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
mins	Minutes
mL	Millilitres
mmol	Millimole
MR	Modified release
MSDS	Material Safety Data Sheet
msec	Milliseconds
NOAEL	No observed adverse effect level
Pgp	P-glycoprotein
PI	Principal investigator
PIS	Participant Information Sheet
PK	Pharmacokinetic(s)
ppm	Parts per million
PsO	Plaque psoriasis
PSRAE	Possible Suicidality Related Adverse Event
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
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}
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
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
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SAS
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 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 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH MCHC %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	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 • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite,			

Laboratory Assessments	Parameters
	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], and hepatitis C virus antibody) at screening only • Tuberculosis test (QuantiFERON) at screening only • C-reactive protein (CRP) at screening only • Anti-nuclear antibody (ANA) in Part B only The results of each test must be entered into the CRF.

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 6 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 Governance 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 workbook 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 workbook 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 authorized 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 authorized 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 CRF 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 CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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 source data verification to confirm that data entered into the CRF by authorized 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 reported on the CRF or entered in the eCRF 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 last visit of the last participant (eg follow-up assessment). 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 jeopardize 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 CRF (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 CRF page. • 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 utilized 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 recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within 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 eCRF (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 eCRF. • 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)

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

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-hormonal 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.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- Refrain from donating sperm for duration of study and for 3 months after study completion or from last dose.
- As there is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male participants, a condom should be used by all male participants during the protocol-defined time frame in Section 6.1.

Female participants

Female participants who are not of childbearing potential do not need to use any methods of contraception.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *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
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If*

not, an additional highly effective method of contraception should be used.)
Sexual abstinence (*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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing will be performed at admission to each study period and at the follow-up visit
- 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 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 CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

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 Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize 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 CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. 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 CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

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

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.

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

Urgent Safety Measures

If Quotient Clinical 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 Clinical may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

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

Reporting of Urgent Safety Issues

Quotient Clinical 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.